FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE MEETING

Friday, March 4, 2016

8:32 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Bldg. 31, Room 1503

Silver Spring, Maryland 20993

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO

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PROCEEDINGS

OPENING REMARKS

DR. LYNFIELD: -- of the Vaccines and Related Biological Products Advisory Committee. And our topic today, of course, is "Strain Selection for the Influenza Virus Vaccines for the 2016-2017 Influenza Season." And I really appreciate everyone's work and expertise because this is such an important issue, so thank you all for coming. I really, again, would like welcome the members of the Committee, the participants, the public, and the audience, viewing the webcast.

I also want to extend a special welcome to Dr. Arnold Monto, who is a new member of VRBPAC. Welcome.

And I also want to note a few things. There are a number of folks, who are going to be joining us by phone today, and this includes Dr. Grohskopf, of the CDC, who will be presenting the U.S. data by phone.

I also want to mention that the Committee should be reminded not to discuss any of the topics outside of the open session, even at breaks, and at lunch. And I also would like to invite the members, consultants, FDA staff at the table, to now introduce themselves, we'll go around, and to state their

institutional affiliations. And so Dr. Sawyer, I wonder if we can start with you.

COMMITTEE INTRODUCTIONS

DR. SAWYER: I'm Mark Sawyer. I'm a Professor of Pediatrics, and Pediatric Infectious Disease Specialist, at the University of California, San Diego.

DR. MOORE: I'm Patrick Moore, and I'm at the University of Pittsburgh Cancer Institute.

DR. LONG: I'm Sarah Long, Professor of Pediatrics at Drexel University College of Medicine in Philadelphia, and Chief of Infectious Diseases at St. Christopher's Hospital for Children in Philadelphia.

DR. MONTO: I'm Arnold Monto. I'm Professor of Public Health and of Epidemiology in the School of Public Health, University of Michigan.

DR. MCINNES: Pamela McInnes, Deputy Director, National Center for Advancing Translational Sciences at the National Institutes of Health.

DR. GRUBER: Marion Gruber, Director, Office of Vaccines, Research, and Review at CBER/FDA.

DR. WEIR: Jerry Weir. I'm the Director of the

Division of Viral Products at CBER/FDA.

DR. DUBOVSKY: My name is Filip Dubovsky. I'm a pediatric infectious disease guy in preventive medicine. I represent the industry. I work for MedImmune/AstraZeneca.

DR. BENNINK: Jack Bennink. The National Institute of Allergy and Infectious Disease Intramural Research Program.

DR. ANDREWS: Ellen Andrews. I'm a consumer representative, visiting for today, and I'm from the Connecticut Health Policy Project.

COL. STANEK: Good morning. Colonel Scott Stanek. Preventive medicine physician; Health Readiness, Policy, and Oversight; Office of the Assistant Secretary of Defense for Health Affairs.

DR. KATZ: Jackie Katz. I'm the Acting Deputy Director of the Influenza Division at CDC, and the Director of the WHO Collaborating Center for Influenza at CDC.

DR. WHARTON: I'm Melinda Wharton. I'm the Director of the Immunization Services Division at the CDC.

DR. AIR: I'm Gillian Air, Professor of Biochemistry at the University of Oklahoma, Health Sciences Center.

DR. GELLIN: I'm Bruce Gellin. I'm the Director of the National Vaccine Program Office at HHS in Washington.

DR. VIJH: Hi. This is Sujata Vijh. I'm the Designated Federal Officer for the Vaccines and Related Biological Products Committee.

DR. LYNFIELD: And Ruth Lynfield and I'm from the Minnesota Department of Health.

Now, let's go to our folks on the phone.

DR. GOLDBERG: Okay. I'm Judith Goldberg. I'm a Professor of Biostatistics at NYU School of Medicine.

DR. LYNFIELD: Great. Thank you for joining us.

DR. GROHSKOPF: I'm Lisa Grohskopf. I'm a medical officer at the Influenza Division, CDC.

DR. LYNFIELD: Anyone else on the phone who is participating?

(No response.)

DR. LYNFIELD: Okay. Well, thank you very much. I appreciate all the introductions. And we look forward to very important discussions today. And now I'd like to turn it over to Dr. Vijh.

DR. VIJH: Thank you, Dr. Lynfield. Good morning everyone. I'm Sujata Vijh. I'm the designated officer for today's VRBPAC meeting. Ms. Denise Royster is the committee management specialist for VRBPAC, and Ms. Rosanna Harvey is our

colleague, also, who is assisting us with the meeting today, and you'll find them seated outside, if you have any questions.

On behalf of CBER, VRBPAC, as well as the Office of Vaccines, we would like to welcome everyone to the 142nd VRBPAC meeting today. As you know, Dr. Ruth Lynfield is the Acting Chair for today's meeting. Dr. Katherine Edwards is the next VRBPAC Chair, and she was unable to make it today, so Dr. Ruth Lynfield is kindly serving as the Chair today.

Today's session has one topic that is open to the public, in its entirety. The meeting topic is described in the Federal Register Notice of January 6, 2016. The FDA and CBER press media contact is Ms. Tara Goodin who is seated in the audience.

Tara, could you please stand up? There's Tara. If the press has any questions, please contact Tara.

Mr. Michael Farkas is the transcriptionist, who is seated right there.

So when the speakers, please, use the microphones, please press the microphone to talk, and remember to switch off when you have finished speaking. Please speak clearly and loudly into the microphone so that the transcriptionist, members of the public, and those participating by phone, audience

listening on the webcast can hear your discussion. Please keep your cell phones and pagers on silent mode.

And during an open public hearing, we request that the people, who would like to make comments, please sign up on the sheet placed here in the center of this aisle, so that we have an idea, and please sign your name, as well as your affiliation.

We request that you, if you'd like to order lunch, please do so at the kiosk outside, at the break, before 10:30 a.m., so that you don't have to wait in line because we have another meeting going on next door.

CONFLICT OF INTEREST STATEMENT

At this point, I'd like to read the Conflict of Interest Statement into the public record: "The Food and Drug Administration is convening today, March 4, 2016, for a meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all participants of the Committee are special government employees, or regular federal employees from other agencies, and are subject to the federal conflict of interest laws and

regulations.

The following information on the status of this Advisory Committee's compliance with federal ethics and conflict of interest laws, including, but not limited to, 18 U.S. Code Section 208, being provided to participants at this meeting, and to the public:

The FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized the FDA to grant waivers to special government employees and regular government employees who have financial conflicts, when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussions to this meeting, members and consultants of this Committee have been screened for potential financial conflicts of interest, of their own, as well as those imputed to them, including those of their spouse or minor children, and for the purposes of U.S. Code Section 208, their employers. These interests may include: investments, consulting, expert witness testimony, contracts, grants, CRADA's, teaching, speaking, writing, patents and royalties, and

primary employment.

For the topic today, the Committee will discuss and make recommendations on the selections of strains to be included in the influenza virus vaccine for the 2016-2017 influenza season. Based on the agenda, and all the financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code Section 208.

Dr. Filip Dubovsky will serve as a temporary industry representative today. Dr. Dubovsky is employed by MedImmune/AstraZeneca. Industry representatives act on behalf of all related industry.

Industry representatives are not special government employees and they do not vote. They may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms.

The FDA asks that in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest. This Conflict of Interest Statement will be available for viewing at the registration table.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

The FDA encourages all other participants to advise the Committee of any financial relationships that you may have with any firms, its products, and if known, its direct competitors."

This concludes the reading of the Conflict of Interest Statement for the public record. I now hand over the meeting to Dr. Ruth Lynfield.

DR. LYNFIELD: Thank you, Dr. Vijh.

I also want to recognize an additional member of the Committee. Dr. Kotloff, will you introduce yourself?

DR. KOTLOFF: Yes. I'm Karen Kotloff. I'm a pediatric infectious disease physician at the University of Maryland, School of Medicine.

DR. LYNFIELD: Thank you. Welcome.

Now, I would like to introduce our first speaker. This is Ms. Anissa Cheung. The Regulatory Coordinator, Division

of Viral Products, Office of Vaccines Research and Review, at CBER/FDA. And I'm wondering if Dr. Cheung can -- thank you very much. Ms. Cheung, thank you very much.

STRAIN SELECTION FOR THE INFLUENZA VIRUS VACCINES
FOR THE 2016-2017 INFLUENZA SEASON

INTRODUCTION

MS. CHEUNG: Thank you and good morning everyone. Today, I'm going to introduce the topics for today's discussions. Okay. The purpose of today's VRBPAC discussions is to review the influenza surveillance and epidemiology data, and also, the antigenic characteristic of the recent ferret sera isolates, the serological response to current vaccines, and the availability of candidate vaccine strain and reagents.

And at the end of the discussions, this Committee the VRBPAC will be asked to vote and make recommendations for the strain of influenza A, both the H1N1 and the H3N2 and B viruses, to be included in the 2016-2017 influenza vaccines license for use in the United States.

So you are going to hear several presentations on the data for the vaccine strain selections. And the types of analysis used for vaccine strain selections that you are going to be reviewing, include the epidemiology of the circulating

strains.

And the CDC folks will present surveillance data from both the U.S., and around the world. You will also hear a presentation on the antigenic relationships among the contemporary viruses and the candidate vaccine strains. And you will hear a presentation from CDC, the Department of Defense, as well as, CBER.

And the types of assays and also techniques that you will be reviewing include the hemagglutination inhibition test using the post-infection ferret sera, and also a hemagglutination inhibition test using panels of sera obtained from humans that have received recent inactivated influenza vaccines.

You will also hear some data on the virus neutralization test, the antigenic cartography, as well as the phylogenetic analysis of the HA and the NA genes of the recent circulating virus, as well as the candidate vaccine virus. You will also hear a couple reports on the vaccine's effectiveness.

There are several challenges for vaccine strain selections. First of all, the vaccine effectiveness depends on how well the match between the hemagglutination of the vaccine, as well as the hemagglutination of the circulating strain of

viruses. However, the antigenic shift; there is an antigenic drift of hemagglutinate that is continuous for both the influenza A and the influenza B viruses, and for the inactivated vaccines, as well as the recombinant protein vaccines, the antibodies to hemagglutination are correlated with vaccine efficacy.

Another challenge is the timeline for the influenza vaccine production. It is relatively fixed, so it is necessary to have to the strain selection done by February and early March, in order to ensure the availability of the vaccines for the subsequent northern hemisphere winter.

In fact, the manufacturers usually begin production of monovalent of one strain at risk before strain selection recommendations are made.

Another challenge is the availability of the reference strain, which we also call "candidate vaccine viruses," which is suitable for vaccine manufacture. And the vaccine production depends on the growth properties of the strain. It depends on how well the strain will be used for manufacture.

In addition, we also need to generate the strain-specific reagents, which are needed for the potency determination for inactivated and also recombinant protein

vaccines. So I would like to show you a graphical illustration, to lay out in detail, month by month, to demonstrate to you how rigid the production timeframe for seasonal influenza vaccines.

So you can see the strain selections have to be done by February or early March, in order to have adequate time for the generation of the referenced viruses, as well as the production of the strain-specific reference reagent, for the blending of the final vaccines, at the end of the day, to ensure that we will have the availability of the vaccines to the public for the northern hemisphere winter.

So we have both, the trivalent and quadrivalent influenza vaccines available in the U.S. There are two antigenically distinct lineages of influenza B that are co-circulating, and they are represented by B/Victoria/2/87 and also B/Yamagata/16/88. And you will hear people refer to it as B/Victoria lineage as well as B/Yamagata lineage.

And currently, we have four quadrivalent vaccines licensed in the U.S. And the current process for selecting an appropriate B strain, for inclusion in the trivalent and quadrivalent vaccines is similar to what we have done over the years for the strain selection for the trivalent vaccine recommendations.

The WHO and the VRBPAC will review the data and make recommendations for each formulation; for trivalent, as well as quadrivalent. And we are expecting to have the same B strain for the trivalent. So I want to quickly refer to the previous recommendations, for the 2015 and 2016 vaccine strain composition, for the northern hemisphere.

Exactly a year ago, the VRBPAC met and they recommended the following strain for inclusion in the U.S. 2015-2016 trivalent influenza vaccines:

For the H1N1 strain, the A/California/7/2009/pdm09-like virus was being recommended, and there was no change from the 2014 and 2015 vaccine recommendations;

For the H3N2 strain, this Committee recommended the A/Switzerland/9715293/2013/H3N2-like virus. And there was a change from the A/Texas/50/2012/H3N2-like virus from previous recommendation;

For trivalent vaccines, the B strain included is B/Phuket/3073/2013-like virus, which is from a B/Yamagata lineage; and that was a change from the B/Massachusetts/2/2012-like virus vaccine recommendations;

For a manufacturer producing quadrivalent influenza vaccines, the Committee recommended a second B strain, which was

B/Brisbane/60/2008 from B/Victoria lineage; and this strain was previously recommended for quadrivalent vaccines in 2014-2015.

The WHO also recommended a vaccine composition for the southern hemisphere for 2016. In September 2015, the WHO met and recommended the following viruses to be used for trivalent influenza vaccines in the 2016 southern winter:

An A/California/7/2009/H1N1pdm09-like virus;

For H3N2, A/Hong Kong/4801/2014/H3N2-like virus; and

For B strain is B/Brisbane/60/2008-like virus, which is from B/Victoria lineage;

It is also recommended that for quadrivalent vaccines containing two influenza B viruses, contain the above three viruses and also a B/Phuket/3073/2013-like virus, which is from B/Yamagata lineage.

So I want to summarize where we are right now.

So a little bit over a week ago, the WHO also met in Geneva, and recommended the vaccine composition for the northern hemisphere 2016-2017. And WHO recommended the following viruses to be used for the trivalent influenza vaccines in the 2016-2017 influenza season for the northern hemisphere:

A/California/7/2009 H1N1pdm09-like virus, which is no change from the 2015-2016 northern hemisphere;

For H3N2 an A/Hong Kong/4801/2014/H3N2-like virus; that is a change from the 2015-2016 northern hemisphere, but this is the same strain recommended for the 2016 southern hemisphere recommendation;

For B strain, they recommend a B/Brisbane/60/2008-like virus from B/Victoria lineage; and that is a change from the 2015-2016 northern hemisphere recommendation; however, this strain was previously recommended for quadrivalent vaccines.

WHO also recommended that for quadrivalent vaccines containing two influenza B viruses, have to contain the above three viruses, and also a B/Phuket/3703/2013-like virus, which is a B/Yamagata lineage; and this strain was previously recommended for trivalent vaccines.

As in the previous year, the national and regional control authority is responsible to approve the composition and formulation of vaccines used in their own country.

So now, I want to pause here, and I just want to let you know that it's the role of this Committee VRBPAC to give recommendations for the antigenic compositions of the 2016-2017 influenza vaccines in the U.S., so I would like to give you some of the options for strain compositions for the 2016-2017 trivalent influenza vaccines:

For influenza A/H1N1, you can either recommend an A/California/7/2009/H1N1/pdm09-like virus, which is the current vaccine strain, or recommend an alternative H1N1 candidate virus;

For the H3N2 influenza A virus, you can either recommend an A/Hong Kong/4801/2014/H3N2-like virus, or recommend an alternative H3N2 candidate vaccine virus;

For the B strain contained in the trivalent influenza vaccines, you have three options:

(a) Recommend a B/Brisbane/60/2008-like virus from B/Victoria lineage; or

(b) Recommend an alternative candidate vaccine virus from the B/Victoria lineage; or

(c) Recommend a candidate vaccine virus from the B/Yamagata lineage.

For strain selections for the second influenza B strain in the quadrivalent influenza vaccines, you have two options:

You can either recommend the inclusion of a B/Phuket/3703/2013-like virus from B/Yamagata lineage; or

Recommend an alternative candidate vaccine virus from the B/Yamagata lineage.

So before I finish my introductions, I would like to flush out the questions from the Committee, for the voting at the end of the discussions. Thank you.

DR. LYNFIELD: Thank you very much, Ms. Cheung.

Are there any clarifying questions from the Committee?

(No response.)

DR. LYNFIELD: Okay. Thank you.

Now, I would like to introduce Dr. Lisa Grohskopf, who is on the phone. And Dr. Lisa Grohskopf is from CDC, and she will be presenting U.S. surveillance data.

DR. GROHSKOPF: Thank you. Can you hear me?

DR. LYNFIELD: Yes. Thank you very much.

DR. GROHSKOPF: Excellent. Thank you so much.

U.S. SURVEILLANCE

DR. GROHSKOPF: Good morning. I'm going to start with the U.S. influenza surveillance update information. This presentation is roughly divided in half; half a surveillance update and half a vaccine effectiveness update. Next slide, please.

So I'm going to start out with some surveillance data for the National Respiratory Enteric Virus Surveillance System

and WHO collaborating laboratories. I should mention, just at the beginning here. The data that I'm presenting here, in this presentation, are from CDC's FluView. And unless otherwise stated, are data for the week seven of the calendar year, which is the week ending February 20, 2016.

I also want to mention that the data are updated each Friday, and so these figures will be updated on the CDC's FluView pages sometime later today.

So first, the U.S. Virologic Surveillance.

This slide and the one following, show results of influenza-positive tests reported to CDC by WHO collaborating laboratories and the National Respiratory and Enteric Virus Surveillance System laboratories, all located in the United States.

This first slide shows result's obtained from the clinical laboratories in the system. In general, these laboratories do not perform subtyping of influenza A viruses.

For our graph, the week of isolation is on the X axis. And on the left Y axis, we have the number of positive specimens, which is represented in the graph by the colored bars. On the right Y axis, we have the percent of specimens submitted that week that were positive, which is represented by

the black lines on the graph.

For the most recent week, week seven, 18,844 specimens were tested, of which 2,599 or 13.8 percent were positive.

Influenza A viruses, which are depicted in yellow have predominated, accounting for 76.1 percent of positive specimens in week seven and overall 69.8 percent of specimens received since October 4, 2015. Next slide.

Now, this slide summarizes the same information, but this time for the public health laboratories rather than the clinical laboratories that were on the earlier slide. These labs generally perform subtyping of influenza A viruses. Some do not, so that's why we still have some yellow representing the un-typed A's up at the top of some of the bars here. And also, some also will check lineage of B viruses.

Again, we see a predominance of influenza A viruses, with H1N1/pdm09 in orange accounting for the majority of these. Next slide.

Next, Virus Characterization of Influenza A Viruses:

Since October 1, 2015, the CDC characterized 660 influenza viruses collected by U.S. laboratories; these included: 271 A/H1N1/pdm09 viruses; 242 A/H3N2 viruses; and 147 influenza B viruses;

All 271 influenza A/H1N1/pdm09 viruses were antigenically characterized as A/California/7/2009-like;

All 242 (H3N2) viruses that were genetically sequenced belonged to genetic groups for which a majority of viruses antigenically characterized were similar to the cell-propagated A/Switzerland/9715293/2013 virus;

Of 109 (H3N2) viruses, also antigenically characterized, 102 or 93.5 percent were A/Switzerland/9715293/2013-like by HI testing, or by neutralization testing. Next slide.

For influenza B viruses, for the 147 of these characterized, all 88 or 100 percent B/Yamagata lineage viruses, were antigenically characterized as B/Phuket/3073/2013-like; 58 of 59 or 98.3 percent of the B/Victoria lineage viruses were antigenically characterized as B/Brisbane/60/2008-like. Next slide.

Next, Influenza-like Illness or "ILI" Surveillance Data from the U.S. Outpatient Influenza-Like Illness Surveillance Network or "ILINet:"

This slide summarizes data from 2015-2016, which is shown in the line with the red triangles and selected previous seasons. The calendar week is on the X axis, and presented

outpatient visits reported to be for ILI are on the Y axis;

ILI is defined as fever, that is a temperature of 100 degrees F or 37.8 degrees C or greater, and cough and/or sore throat;

Nationwide, during week seven 3.2 percent of outpatient visits reported through this system, were due to influenza-like illness. This percentage is above the national baseline of 2.1 percent. Next slide.

This slide summarizes hospitalization data from FluSurv.NET:

FluSurv.NET covers more than 70 counties in the ten Emerging Infections Program or "EIP" states, which are: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee, and additional Influenza Hospitalization Surveillance Project or IHSP" states;

Between October 1, 2015, and February 20, 2016, 1,594 lab-confirmed influenza-associated hospitalizations were reported;

The overall hospitalization rate was 5.8 per 100,000-population;

The highest rate of hospitalization was among adults, age greater than or equal to 65 years, at 16.7 per 100,000-

population, and adults age 50 through 64 years, at 7.4 per 100,000-population;

Among all hospitalizations, 72.6 percent were associated with influenza A; 25.7 percent with influenza B; 1.3 percent with A and B co-infection; and 0.4 percent had no virus-type information;

Among those with influenza A subtype information, 89.0 were age A/H1N1/pdm09 and 46 or 11 percent were A/H3N2 viruses. Next slide.

This figure depicts Surveillance of Pneumonia and Influenza-Associated Deaths;

These data come from the National Center for Health Statistics Mortality Surveillance System. In this case, these data are from slightly earlier; the week ending February 6, rather than February 20 of the calendar year, so this is really more like week five data:

For week five 6.6 percent of deaths occurring, reported to this system, the week ending February 6, 2016, were due to pneumonia and influenza. This percentage is below the epidemic threshold of 7.7 percent calculated for week five. Next slide.

This slide summarizes Pediatric Deaths Associated with

Laboratory-Confirmed Influenza, which has been a reportable condition since 2004; the graph depicts information from the 2012-2013 season, that's the cluster of bars on the far left, to the present season 2015-2016, the smaller cluster of bars on the right:

Thus far, a total, as of this week, of 14 influenza-associated pediatric deaths have been reported during the 2015-2016 Season. Next slide.

This is the last surveillance slide and it summarizes Influenza Activity Reported by State and Territorial Epidemiologists; it describes geographic spreads of influenza viruses, but does not measure severity of influenza activity:

During week seven, widespread influenza activity was reported by Guam, Puerto Rico, and 21 states;

Regional influenza activity was reported by 18 states;

Local influenza activity was reported by the District of Columbia and 10 states; and

Sporadic influenza activity was reported by the U.S. Virgin Islands, and one state. Next slide.

In summary, for the surveillance part of the talk:

Influenza activity, to date, is low, as compared with the previous most recent three seasons;

Rates of influenza-associated hospitalizations are lower;

Pneumonia and influenza mortality has not exceeded threshold levels;

Influenza A/H1N1 viruses have predominated, but A/H3N2 and B viruses of both lineages have co-circulated;

The majority of viruses are similar to the current vaccine viruses. Next slide.

So changing gears now and moving on to Interim Estimates of Influenza Vaccine Effectiveness for this Season:

These data are from the U.S. Influenza Vaccine Effectiveness, or U.S. Flu VE Network, and they were presented recently at ACIP, which had a meeting on February 24, 2016;

These are preliminary interim estimates and have not yet been published;

These particular interim estimates included patients enrolled from November 2, 2015, through February 12, 2016. Next slide.

Methods used by the U.S. Flu VE Network have previously been described; methods used to produce these interim estimates were the same as those used for interim estimates in previous seasons:

Briefly, outpatients 6 months-of-age and older, with acute respiratory illness and cough of seven or fewer days duration, were enrolled at the five U.S. Flu VE Network sites, from November 2, 2015, through February 12, 2016;

A test negative case control design was used to estimate vaccine effectiveness, by comparing vaccination odds among influenza RT-PCR positive cases, and RT-PCR negative controls;

Vaccination status was defined at the receipt of at least one dose, of any 2015-2016 seasonal influenza vaccine, according to medical records, immunization registries and/or self-report;

Vaccine effectiveness is estimated as one minus the adjusted odds ratio times one hundred;

Variables included in the models for adjustment are those listed. Next slide.

From November 2, 2015, through February 12, 2016, a total of 3,333 outpatients were enrolled at the five network sites:

Three thousand eighty-one or 92 percent were RT-PCR negative for influenza;

Two hundred and fifty-two or 8 percent of enrolled

patients were influenza-positive;

Distribution of influenza cases by type and subtype is shown: both influenza A and B viruses circulated with the majority of influenza A viruses being H1N1/pdm09; and the majority of B viruses belong to the Yamagata lineage. Next slide.

This epi curve shows the number of enrolled participants with RT-PCR-confirmed influenza A or B, by epidemiologic week of enrollment and the percent positivity for any influenza type by week; note that laboratory testing is incomplete for patients enrolled during epidemiologic week six:

Few cases were enrolled before the first week of January, with a low percentage of those enrolled being positive for influenza A or B during most weeks. Next slide.

Interim-adjusted estimates of vaccine effectiveness against medically-attended influenza for all patients, age 6 months and older was: 59 percent with a 95 percent confidence interval from 44 percent to 70 percent. Next slide.

Interim-adjusted vaccine effectiveness against H1N1/pdm09 for all ages combined was: 51 percent with a confidence interval from 25 to 69 percent;

Adjusted estimates of vaccine effectiveness against

influenza B for all ages combined was: 76 percent with a confidence interval from 59 to 86 percent, and was similar against B/Yamagata lineage viruses at 79 percent. Next slide.

In summary, interim results from the U.S. Flu VE Network for the 2015-2016 season, based on enrollment through February 12, 2016, indicate vaccine effectiveness of 59 percent against medically-attended influenza. The interim estimate for this season is similar to that of previous seasons when vaccine was well matched to circulating influenza viruses.

Significant protection against circulating influenza H1N1/09 and B viruses was observed for all ages combined, while VE was not estimated against the (H3N2) viruses, due to the small number of cases. Enrollment in the network continues.

Interim estimates, it must be said, are less precise due to the low numbers of flu cases enrolled, and end of season VE estimates may differ from these interim estimates. Next slide.

That concludes my presentation. I'd be happy to take any questions. Thank you.

DR. LYNFIELD: Thank you very much, Dr. Grohskopf.

Are there clarifying questions? Yes?

QUESTIONS:

DR. BENNINK: In the vaccine effectiveness, is all of that inactivated vaccine?

DR. GROHSKOPF: That is all vaccine. There is, at this point, not sufficient information to be able to split data out. As we've had relatively low numbers of cases, and relatively low enrollment, given that the season's been a bit slower than usual. I anticipate though, that information you know should -- hopefully there should be enough cases in either group to be able to split that out eventually.

DR. LYNFIELD: Dr. Grohskopf, I have a question; if we could go back to slide three? I am wondering, what proportion of B lineages are not characterized in that data set? Do you have a rough ballpark?

DR. GROHSKOPF: I don't actually have that number in my head. I don’t know if Dr. Katz is aware of it. Those data are represented by the dark green.

DR. LYNFIELD: Yes.

DR. GROHSKOPF: And you know it's -- obviously, that proportion has increased somewhat, the overall number of isolates have increased, but I actually don't know the precise number. I can attempt to get that during today, though.

DR. LYNFIELD: You know I think that would be helpful because one of our questions is to choose the lineage for the trivalent vaccine. And in looking at these data, it does appear that the Yamagata lineage is making up a larger proportion than the Victoria lineage. And so I think it would be useful to have the proportion that is not characterized.

DR. GROHSKOPF: Okay. I will obtain that this morning.

DR. LYNFIELD: Dr. Monto?

DR. MONTO: On slide four, you state that the (H3N2) isolates are similar to the cell-propagated A/Switzerland. Are we going to be hearing more about this issue, and the clades, and everything else, because we're talking about a change, and why a change, if everything's the same?

DR. GROHSKOPF: I believe that will be covered in the data presented by Dr. Katz.

DR. LYNFIELD: Dr. Sawyer?

DR. SAWYER: Lisa, its Mark Sawyer. I noticed that well, in 2009, when (H1N1) first began to circulate, it was the younger adult population and pediatric population that had the majority of disease. I notice from your epi curve, this season so far, even though (H1N1) is the predominate A strain that the

senior 65 and above are now more prominently featured with medically-attended visits.

Are the numbers sufficient this year, so far, that you anticipate that trend continuing? And if so, do you care to speculate why, now, seniors are being more affected than younger adults?

DR. GROHSKOPF: Difficult to speculate always, of course. That is a great question. We did also, see sort of the older/younger adults and the younger/adult older/adults those groups of just below 65 and older, somewhat, were susceptive during the 2013-2014 season with regard to hospitalizations, for example, than they had in previous seasons, and 2013-2014 was also an (H1N1) predominant season.

Difficult to say, really, I don't personally have an explanation. Overall, the season did get off to a somewhat later, slower start. It may be that we just are not seeing sufficient numbers. I really do not have an explanation for that.

DR. LONG: Hi Lisa. Sarah Long. I know your definition of immunization, or vaccination was at least one dose of the 2015-2016 seasonal flu vaccine, but if we think about the circulation of pandemic 09, for the last several years, and the

immunizations in the last several years containing that, do you have any idea, or a speculation about how you might see decreased vaccine efficacy because of widespread previous immunization, or previous experience of those who are not vaccinated this year? A complicated question, sorry.

DR. GROHSKOPF: Yes. I'm not exactly certain how to address that. Of course, as those in the room know, H1N1/pdm, or A/California/7/2009, has been present in the vaccine for some time. Among those vaccinated repeatedly, they would have had repeated exposure to that virus.

I guess one thing, I would want to be cautious about is that the estimate that we're seeing now is, again, preliminary and based on relatively fewer cases than we normally have by this time of year. So I think it's you know at the end of the day, going to be important to see what bears out in the end as the season continues, and also once these data are more finalized.

At present, for example, by the end of the season, records have been gone through and self-report is less of an issue, but up until this point as the season is going through, particularly this early, immunization data is at least partially self-report, by a greater proportion, with a somewhat lesser

proportion than there will ultimately be, coming from more definitive sources.

Also again, we should in theory at least, have greater numbers as time goes on. So I guess I would just be cautious about understanding that these estimates are preliminary.

DR. LYNFIELD: Dr. Kotloff.

DR. KOTLOFF: Hi. It's Karen Kotloff. I notice that your case definition was, "recipients of at least one dose," but we know that for young children, the recommendation is for two doses during the first vaccination series. And I'm wondering what impact, you think were you to include young children who had received the requisite two doses, what impact that would have on your measured vaccine effectiveness?

DR. GROHSKOPF: I think at this point, it is difficult to predict that. That information normally becomes available more toward the end of the season. At this point, there actually isn't even really sufficient data to break the cases down by age distribution. So it would be difficult to speculate on that right now.

DR. LYNFIELD: Dr. Moore?

DR. MOORE: Lisa, can you give us a little bit more information on the (H3N2) vaccine efficacy, which you didn't

include in this presentation because the number of cases were so small, but if we're going to be changing the vaccine component, I'd like to get, at least, a little sense of, if we know where the numbers are going, if we had enough numbers.

Were all 25 cases that were (H3N2) positive? Were they unvaccinated or was it evenly distributed? Just, a little bit more information on that.

DR. GROHSKOPF: I actually don't have that information at hand, but I can put that on the list with the other questions that came up about the distribution of B viruses in the Virologic surveillance. And I will be on the phone all day, for the entire meeting. So I will obtain, see if I can learn anything else about that during the break, if that's all right.

DR. LYNFIELD: Thank you, Lisa, very much.

Are there any additional questions?

(No response.)

DR. LYNFIELD: Okay. Thank you very much, again.

DR. GROHSKOPF: Thank you.

DR. LYNFIELD: Now, I'd like to introduce Dr. Jackie Katz, who will be presenting next. And Dr. Katz is the Deputy Directing (Acting) of the Influenza Division, as well as the Director of the WHO Collaborating Center for Surveillance,

Epidemiology, and Control of Influenza, at the CDC. And Dr. Katz is going to be speaking on world surveillance and virus characterization.

DR. KATZ: Thank you, Dr. Lynfield.

Okay. So I'm going to be providing a summary of the data that was presented last week at the WHO Vaccine Consultation Meeting, for which the decision you've already seen, was made for the WHO recommendations for the northern hemisphere 2016-2017 influenza vaccine.

WORLD SURVEILLANCE/VIRUS CHARACTERIZATION

DR. KATZ: So surveillance, globally, for influenza, is coordinated by the WHO Global Influenza Surveillance and Response Network, also known as "GISRS." And as you can appreciate, this is a year-round process, whereby, national influenza centers and WHO Collaborating Centers, together with the ERL's, the Essential Regulatory Laboratories, and other reference laboratories, are continually performing surveillance for seasonal and novel influenza viruses.

So as we've heard earlier from Ms. Cheung, there was a decision for the southern hemisphere strain selection for 2016, and that was made last September.

So last week, the consultation included the review analysis and a conclusion, over a three-day period. The meeting was chaired by Dr. Yuelong Shu, from the China CDC, the WHO Collaborating Center there, and included the nine advisors, which represent the directors of the 6 WHO Collaborating Centers, and directors of three essential regulatory laboratories. There was also, another, about 25 people from other national influenza centers, from other members of the WHO Collaborating Centers, and ERL's, as well as academic partners, and our partners from the veterinary sector, and other national authorities.

So we've already heard that in September, the WHO recommendations changed, and I just want to highlight why that was done. The changes that were made were for the (H3N2) component, which changed to A/Hong Kong/4801/2014; it was previously Switzerland, for the 2015 southern hemisphere strain.

And that was really done, not because there was recognition of antigenic drift, but because by September 2015, there was availability of appropriate candidate vaccine viruses, that more closely matched the genetic subgroup of circulating viruses, and that virus was represented by the Hong Kong/4801, so it was seen as sort of an incremental improvement for the

(H3N2) component. The other change that was made was, to swap the B lineage viruses around, and that was done in response to a notable expansion of the B/Victoria lineage, represented by the B/Brisbane/60/2008 component, and so it was felt that it was more critical to have that B lineage in the trivalent inactivated vaccine.

So moving on now to the data that we had for our consultation and decision process last week. This is a WHO slide showing the percentage of respiratory specimens that tested positive for influenza by their transmission zones. And there are two things to notice on this map.

First, is the shading, where you can see that shading goes from sort of white, to light yellow, to a darker green, and that represents an incremental increase in the number of influenza positives. So you can see in North America, most regions of North America, the activity and the numbers of viruses isolated were lower than in some regions of Europe and Asia. And then the pie charts represent the actual breakdown of viruses by subtype and by B lineage.

And if you'll focus on the light blue, that's the H1N1/pdm09 viruses, and you can see that they predominated in many regions of the world. And this is shown here, over a time

series. This is the numbers of influenza viruses by subtype that were identified globally to WHO, over the past year.

And as you can see, in sort of the late December, towards the end of 2015, these numbers started to increase as the northern hemisphere season took off, and is still sort of peaking around this time. You can see, again, that the light blue color represents the H1N1/pdm09 viruses, and they represented the majority of viruses, and that's shown a little more graphically here. You can see that about three quarters of the viruses reported to WHO were influenza A, and of those, the majority were (H1N1) with a smaller proportion being the influenza B viruses.

So I'm going to talk now, first of all, about our characterization of the H1N1/pdm09 viruses. So this is another WHO slide that shows the activity level of (H1N1) worldwide since September through, to early February. And what this map represents is, actually it's sort of a heat map showing the maximum activity reported over that time.

So we see that there are still some late season southern hemisphere activity shown in Chile, and other regions, for the southern hemisphere. But over the northern hemisphere season, you can see that there was quite a lot of (H1N1)

activity, predominantly in parts of Europe, Africa, Asia, and also widespread activity in North America, somewhat less so, more localized activity, reported in the United States at that time.

And just showing you another way, in looking at this in terms of the last few seasons, you can see the red line, which are (H1N1) viruses detected by the global system. For 2016, you can see that the number is quite high, and approaching what was seen, in a big (H1N1) season in 2014, and much higher compared with the black line, which was the 2014-2015 season in the northern hemisphere.

So now we're going to start getting into some of the technical genetic and antigenic data. And this is a tree of the phylogenetic relationships of the hemagglutinin genes of representative (H1N1) viruses. The color coding reflects the month. And so the viruses colored in orange and pink, are the most recently isolated or collected viruses, from January- - February; in the green, are from December.

One thing to note is the current vaccine strain; California/7/2009 is located here, and for the past several seasons, we've seen that a group of genetic group 6B viruses have predominated. But this season, we've seen quite the rapid

emergence of two genetic subgroup's within 6B, and these are the 6B1 viruses, which have these key amino acid changes at residue's 84, 162, and 216 in HA1. And the change at 162 confers a glycosylation motif, which means that this site might have a glycosylation added to it. And you can see that many of the viruses are in this 6B1 cluster.

I know it's not possible to read this, from where you are, but I do want to note that we have a number of viruses, and this is true for all of our trees, that are annotated USAFSAM. And this represents sequence's that have been contributed to the system by our Department of Defense colleagues here in the U.S. And these data are very useful to enrich, not only the data we have for domestic viruses, but also from different international sites. And you can see that -- well, you may not be able to see, but I will tell you, that the viruses in the 6B1 group are really from all parts of the world.

And similarly, there are also viruses from different parts of the world, which fall into this smaller group; the 6B2 viruses. And they have represented genetic changes at residues 152 and 173, which are in the head of the HA1 molecule, and at 491 and 501, which are in the more-conserved HA2 region of the molecule. So there are a smaller number of viruses here, but

geographically, most regions detected small numbers of these viruses, also of the 6B2 group, with the exception of China, that detected many such viruses, and you'll see the global distribution in a further slide.

So this is also another way that we present the data. This is done by our University of Cambridge modeling colleagues. And so what they do, is they take all the genetic data for the HA genes, that are available in our databases, and do a time series over the last 11 months. And this has enabled us to really see the rapid emergence of the 6B1 viruses.

Each virus is represented by a bar; they're color-coded by the regions of the world that they come from. But the main point I want to make here, is these last five or six months since October, we've seen this very rapid emergence of the 6B1 viruses. The 6B2 viruses are down here; there's far fewer of them, and they've really emerged since about July, of last year.

So we also look at the neuraminidase gene, and really there are no dramatic changes there, but this is just to note that, as for the hemagglutinin, the viruses are clustering into different genetic subgroups.

So this is another way to look at the geographic distribution of the (H1N1) viruses this season. And we can see,

shown in orange, is this new genetic subgroup of 6B1 viruses. And so it's very easy to see, that these viruses have been predominating, in the viruses circulating in Europe, in North America, and even in Oceania; although, the numbers are very small because this isn't their flu season. We also see them in Asia, but in Asia, there's also a substantial presence of the 6B group, and this is largely driven by the predominance of the 6B2 subgroup in China. We're still seeing 6B viruses in South America, and in Africa, but to a lesser extent.

Okay. I'm going to go through the first hemagglutination inhibition test quite slowly. We've got some more of these for the other influenza types and subtypes. So I just want to orient you to what we do here.

So the hemagglutination test, tests the ability of referenced panels of ferret antisera. And these are sera that are raised, by infecting naïve ferrets, with the particular virus in question. And ferrets make a very strain-specific response, and they can uniquely characterize changes, antigenic changes, in the hemagglutinin.

So the test measures the ability of these antibodies present in the ferret's antisera, to block the interaction between the virus and red blood cells. In this case, it's

turkey red blood cells, to which the virus binds through the hemagglutinin. So the way this test is set up, is we have different reference sera across the top. Shown highlighted here, is the vaccine virus California/07, both an egg-grown version and a cell-grown version; the homologous viruses under the reference antigens, and so, the titer to its homologous viruses, highlighted in red.

So we also have broken down the test viruses here, and these viruses, many of them are from the U.S., they're also from Central and South America and Asia, and a few from Europe. We're showing the breakdown of the genetic groups here, and these are the actual changes, but you can see that there are many 6B1 viruses, and that's because that's primarily what we saw circulating in the U.S.; still some 6B, and the occasional 6B2.

So when we look at how the test viruses react to the sera, relative to the titer that we see, by, we get with the homologous virus, we see for the California vaccine virus, that all of the circulating tested viruses, are reacting to titers that are very comparable to the homologous titers. So that tells us that we're not really seeing any antigenic change, compared with the California/07 vaccine virus.

To further look at the antigenic properties of these newly-circulating 6B1 and 6B2 genetic groups, we raised antisera to representative viruses: the Michigan/45 virus for 6B1 and a Minnesota/32 for the 6B2 groups. And these are highlighted in the pink colors. And again, when you compare -- first of all, these viruses are reacting comparably with the California/07 viruses, themselves, or these antisera are, and also they're really, reacting very well with all of the circulating viruses.

So this tells us that these viruses, even when we look at this in two ways, are not antigenically any different from the California/07 viruses. So to look at this by another test, we really wanted to confirm that the HI was showing us that there were no antigenic differences. And so, on occasions we have also used neutralization assays; we use these quite a lot for the (H3N2) viruses.

So this is a neutralization assay that was performed by the London WHO Collaborating Centre, known as the Crick Institute. And this table is set up pretty much the same way that the HI was. There are a more limited number of reference antisera raised in ferrets, across the top, they're homologous viruses. And the homologous titer's shown in red.

And then a number of circulating viruses that were

tested; these are from Europe. There's some from Iran, and one from Africa in here. And again, these represent the circulating viruses, some 6B1 virus; mostly 6B1, and one 6B2 here.

And we're essentially seeing the same result that we saw with the HI. Antisera raised to the California vaccine virus is reacting very well, and are comparable titers, in most cases, for the circulating viruses. And when we raise an antisera to one of these new genetic subgroups, this is a virus called "Slovania," we're seeing again, that compared with the high homologous titer here, the circulating viruses are well covered by this antisera.

We also do antigenic cartography, and this is done, again, from our University of Cambridge colleagues. And they are provided all of the HI data, from the WHO Collaborating Centers. And in this particular depiction, the big red dot in the middle represents the California/07 cell-grown; the egg-grown is the green a little further away.

And what's being done here, is, there's color-coding for the two genetic subgroups that we're currently seeing. So in blue, is the 6B1, and in pink, is the 6B2. And you can see that there's really, quite a tight clustering of these viruses around the California/07 viruses, indicating that these viruses

are all antigenically very similar.

And then this is just the final information. This is a compilation of the HI data, from all of the WHO Collaborating Centers. You can see over 800 viruses were tested. And 99 percent of the viruses were antigenically characterized as being California/07-like.

In summary, H1N1/pdm09 viruses were the most frequently detected virus globally. The activity for (H1N1) was generally higher than in the previous season, and there were local-to-widespread outbreaks in many regions of the world. Can you go back, please? Thanks.

And you may have heard reports in the media that there were reports in Europe, from the Middle East, and also we've had reports at CDC from the U.S., where there have been severe and fatal cases reported. And that is really what we've seen in previous years, when (H1N1) has circulated. And particularly, in this year we know that about 50 percent of the H1N1/pdm09 viruses, the age range in 50 percent of those cases, has been in the younger to middle-age adult, in that 24 to 50-plus age group.

Of note this season, we have two new genetic sub-clades that have emerged rapidly within the 6B group. The 6B1

viruses have expanded and are predominating in many countries of the world. The 6B2 viruses have been detected at lower levels in many countries, but are predominating in China. But antigenically, all of these viruses remain similar to California/7/2009.

We've also evaluated the neuraminidase inhibitor activity, and the vast majority of (H1N1) tested were sensitive to all of the neuraminidase inhibitors. So I'm going to move on, to the (H3N2) viruses. This is the map of the world.

There's overall, lower activity. And again, some of this activity is the late season from the southern hemisphere, but there was some, local-to-widespread activity in North America and Asia, and a few parts of some countries in Europe and Africa.

And this sort of puts the influenza A activity this season into perspective, particularly with last season, which is shown in the black line. And you can see this is the current season where there are overall, quite a small number of viruses detected by the global influenza system.

Here again we have a phylogenetic tree of the hemagglutinin gene. And the main point here is, as we saw last season, we have several different genetic subgroups circulating.

And the 3C2A viruses, in particular, continue to predominate globally.

We've had a small resurgence of the 3C3A viruses. And I'll remind you that the Switzerland/2013 vaccine component, from our 2016-2017 season is a 3C3A virus. And then we have some very low-level circulation still of the occasional 3C3 and 3C3B virus. So the Hong Kong/4801 virus that was selected for the southern hemisphere 2016 is a 3C2A virus, and you can see it highlighted here.

So among the recent viruses, there are two emerging groups that have genetic changes. One is a group that has changes at residues 142 and 197 in HA1, and many of these viruses also have a change at 168. There's another group that is expanding at this time, which has a substitution at 171, and then several substitutions in HA2.

And when we look, we've been working with some modelers to understand the trajectories and the expansions of some of these subgroups. And we can see that the 171 group is predominating in Asia and in North America, and continues to expand at the moment. And there's also some expansion, to a lesser extent, of this 142/197 group. So these are the groups that I just want to highlight because we're also looking at them

antigenically, to see if they've changed at all.

This is another time series and this, just again, graphically shows that really the 3C2A viruses are really still predominating worldwide. There was as I mentioned, a slight resurgence of 3C3A in Europe this season and very rare, if any, circulation of the 3C3 and 3C3B in the northern hemisphere.

This is the neuraminidase gene, and again, the groups that are defined by the hemagglutinin. You can see that the viruses also break out into these groups for the neuraminidase gene.

So looking at the global expansion, you can see a sea of orange, and that tells you that the 3C2A viruses are predominating in all parts of the world. As I mentioned, there were some lower-level re-emergence of the 3C2A viruses, shown in purple, in Europe, in the northern hemisphere, and then there was also some activity in South America, and very little 3C3, shown in the red, and 3C3B in the pink.

So before I talk about the antigenic characterization of (H3N2) viruses, I just wanted to remind you that these viruses have some very unique properties at the present time, which makes them very technically difficult to do our standard HI assay. First of all, we grow the viruses in mammalian cell

culture. Many of these viruses after repeated passage acquire mutations in the neuraminidase at residues 151 or 148, and this has been shown to enhance the ability of the neuraminidase to actually bind to red blood cells. And so, that means that if we just do a standard HI test, we don't know if when measuring antibody to the neuraminidase, or antibody to the hemagglutinin.

So to rule out the binding to the neuraminidase, we add the neuraminidase inhibitor, oseltamivir, and that eliminates the binding ability of the neuraminidase, so we know we're only testing antibodies that are binding the hemagglutinin, and only characterizing that response. In addition, in the last 18 months or so, many of the predominantly circulating viruses, these 3C2A viruses, have, although they will grow in cell culture, they bind the red blood cell receptors very weakly. So we actually can't do hemagglutination inhibition testing on about two thirds of the virus.

At CDC, we are able to test about one third of the viruses that we grow in culture. And so we've been implementing alternate assays, including the virus neutralization assay, and so you'll see some virus neutralization results. In addition, the 3C2A viruses have a glycosylation motif at the head of the molecule, and with repeated passage in cell culture, all with

growth in embryonated eggs, they may lose this glycosylation.

I should say though, that for the majority of viruses that we've tested at CDC by hemagglutination inhibition, we do very limited passaging in cell culture. And over 80 percent of the viruses have retained that glycosylation, so they do look like the viruses, or like the sequence that we would get out of an original specimen, out of the human.

So first of all, I'll show you a neutralization assay. And this is again, data from the London Collaborating Centre. So highlighted by the red bar, is the response of circulating viruses. So this is set up the previous way of the previous slides.

So across the top is, antisera to reference ferret antisera. They're homologous viruses, and the homologous titers shown in red. And then a number of circulating viruses; this is mostly from Europe and Asia, and again, the different subclades that these viruses belong to. And you can see a predominance of 3C2A, here.

And so if we look at this highlighted red box, here on the right-hand side, this is ferret antisera raised to sell propagated Switzerland. And you can see that with a homologous titer of 160, that most of the circulating viruses have titers

that are within four-fold, and indeed within two-fold of this homologous titer, indicating that they are well-covered by this antisera to Switzerland.

If we look at the next red bar here, over on the left-hand side, this is now, antisera, raised to sell propagated; it's a Hong Kong/4801-like virus. It's not 4801 itself, because of problems that we had in actually culturing the 4801 virus in cells. So this is a surrogate for Hong Kong/4801-like virus.

And you can see, again, that the majority of viruses, of the circulating viruses tested, are well-covered by this antisera. And then shown in yellow is the results of the antisera raised to the egg-propagated Hong Kong/4801 virus. And most of the viruses are within four-fold titers of this homologous titer; although, there are some reductions here. And we particularly see reductions with the 3C2A viruses, and I'll point that out a little more in the next test.

And this is another neutralization test. This is now done at the CDC. We call it something slightly different, but it's essentially a very similar neutralization assay as to the one used in London.

The tables are set up the same way. And you can see at the top, here, for our circulating viruses, we have a number

of viruses that are in this box that belong to the 3C3A group. So highlighted in yellow, are the antisera to the Switzerland viruses, both the cell-propagated and the egg-propagated viruses, and again, you can see antisera to the cell-propagated reacts very well, or within four-fold of the homologous titer, with circulating viruses. The antisera to the egg-propagated virus, does this a little less better, because it has a high homologous titer.

If we look at the antisera raised to the 3C2A referenced viruses, and these are the Hong Kong/4801 cell-propagated and Hong Kong/4801 egg-propagated viruses, you can see again that the antisera to the cell-propagated virus gives titers to the circulating 3C2A viruses that are within four-fold of this homologous titer. The responses, as I said, to the 3C3A viruses, they're not as well-covered by antisera to the 3C2A viruses.

And then when we look at this using antigenic cartography, you can see -- this is data from the CDC neutralization assays -- you can see that by this approach, the viruses are really clustering around the Hong Kong/4801 reference viruses here, and 3C. So the 3C2A viruses are color-coded in red and they're clustering around the 3C2A Hong

Kong/4801 virus. Obviously very small numbers of 3C3A viruses shown in green and they're clustering more around the Switzerland virus. So although we're not seeing a real antigenic drift, we can distinguish between the 3C3A and 3C2A viruses.

And this is a small HI test performed at CDC. One thing I didn't mention in the early tables, but is also true for this HI table, is, when we look at the viruses that have the genetic changes that I referred to earlier, either the 142 or 197 changes, or some viruses with the 171 changes, we're not seeing anything antigenically different, really, about these viruses.

There is one virus here from Canada that is somewhat a low reactor, but we believe that's because it has some other unique changes in the hemagglutinin. So overall, although we're seeing genetic changes, as we would expect in the (H3N2) viruses, antigenically we're not seeing big differences in any of these viruses that have these signature changes. And this is shown again graphically.

So this is all of the CDC HI data that we have. And similar to the neutralization antigenic cartography, you can see that the 3C3A viruses shown in green -- and this is a time

series, so this is data from the last year, I believe -- you can see that, although the 3C2A in red and 3C3A in green are overlapping, the majority of 3C2A viruses are clustering more around the Hong Kong/4801 virus, versus the Switzerland virus.

Was that, my time is up? No? Okay. I thought I heard a bell go. Good. Okay. I've got time.

So what I'm going to show you in the next couple of slides, is, all the HI data, from all of the collaborating centers. The total number of viruses at the bottom is going to change on each of the tables, just because at different times, different centers, we're using different antisera to characterize their viruses.

But if we look at antisera raised to the cell-propagated Switzerland -- and I'll remind you that we have to look at the antisera raised to a cell-propagated virus, because most of our, or all of our test viruses, all of the circulating viruses are grown in cells. And that's the best way to really determine, whether there's antigenic drift occurring in the circulating viruses.

We also compare results against egg-grown viruses, and we do that because we have to propagate the viruses in eggs, in order that we have a suitable candidate vaccine virus. But for

all influenza viruses, but particularly for (H3N2) viruses, egg propagation leads to changes that may introduce some antigenic changes. So first of all, I'm going to show you this table, where you can see that -- can you go back to the previous table?

So compared with the antisera raised to Switzerland cell-propagated reference virus, the vast majority of the almost 500 viruses tested, 97 percent remain similar to Switzerland, which was the component of our vaccine this past season. And there was a low proportion of what we would call "low reactors."

If we look at that in the same way, but now look at antisera raised to the 3C2A virus Hong Kong/4801, we see the same thing, which tells us that these viruses are really -- the 3C2A and the 3A, they're really not antigenically distinct. The majority of viruses are also well-covered by antisera raised to cell-propagated Hong Hong/4801.

If we now look at how circulating viruses react with sera raised to egg-propagated Switzerland or Hong Kong, we see that there's a trend towards the proportion of viruses that are well-covered, or maybe I should refer to the ones that are not reacting well with this antisera. So that's this column. We refer to them as "low reactors."

They have titers that are reduced by at least eight-

fold to the homologous titer to Switzerland, and we can see that we've got about 57 percent of the circulating viruses that were tested by the different labs. However, if we look at the same thing for Hong Kong, we can see that the antisera to the Hong Kong/4801 3C2A virus, does a better job. There are a lower proportion of viruses that are low reactors to this antisera, suggesting that for an egg-propagated potential vaccine virus, the Hong Kong/2014 viruses are providing better inhibition and better coverage than are the Switzerland-like 3C2A viruses.

So in summary, there was, overall for (H3N2), there was fairly low activity, particularly in relation to last season and other seasons. The 3C2A viruses are now predominating in all regions of the world, and the subclade 3C3A, although there was a small resurgence in Europe, and the 3C3B viruses are really circulating at quite low levels.

So most of the recent 3C2A viruses were well-inhibited by ferret antisera raised against either the cell-propagated reference Switzerland virus, or the Hong Kong virus. But I did show you that the antisera to the 3C2A virus Hong Kong/4801-like viruses, tended to have somewhat reduced inhibition against the small number of 3C2A viruses that we could test. So we can discriminate antigenically between these subclades in some

cases, but overall, they remain antigenically closely related. When we look at ferret antisera raised to the egg-propagated viruses, we see that the 3C2A virus, generally inhibit recently circulating viruses better than antisera raised to the egg-propagated Switzerland/2013 viruses, and then finally, again, we really didn't see much evidence of resistance to the neuraminidase inhibitors for the (H3N2) viruses.

So moving on to influenza B, this is, again, the heat map from WHO, and you can see that there was some circulation of influenza B viruses. And again, some of this is the late southern hemisphere circulation, in the southern hemisphere, in Oceania, and South America, but there was some activity in North America, and in parts of Asia, and Europe, and Africa.

And so again, relative to previous seasons, you can see overall that the 2016-2017 season in the northern hemisphere for influenza B viruses, has been quite modest compared with the previous several seasons, particularly 2015, in black.

And geographically, the distribution of the B/Yamagata and B/Victoria lineages has changed. And so shown in orange, are the B/Victoria lineage viruses, and you can see now that they are predominating in many regions of the world. In Australia and New Zealand towards the end of their southern

hemisphere season, the B/Victoria lineage really overtook the B/Yamagata lineage.

The same thing was happening in South America. It's very evident in Europe. It's in Asia and North America. The B/Yamagata lineage shown in the blue is still predominating, but we have seen an increase in the proportion of B/Victoria lineage viruses this season in the United States.

So I'm going to first talk about the B/Yamagata lineage viruses, and here's the genetic information from the hemagglutinin. And just to point out, the B/Phuket/2013 vaccine virus component is here, it belongs to the Y3 lineage, and you can see that the vast majority of recently circulating viruses around the globe belong to this Y3 lineage, and there's just a very small number we detected.

We received some viruses from Africa that still were the Y2 lineage, but this lineage, essentially appears to be dying out. And this is one of the reasons that B/Phuket was chosen a few seasons ago, to represent the B/Yamagata lineage. So most of the circulating strains have this cluster of genetic changes, and you can see some other changes spread out, but there's really no further definition of genetic subgroups emerging within the Y3 group.

And this is just a time series. And it really emphasizes that there was a lot of B/Yamagata virus activity in the previous six months. And there's been a lower level of activity in the current, just past six months, in all regions of the world.

The neuraminidase tree there's really nothing remarkable. I should go back and highlight. I forgot to mention that we continue to see the persistence of some interesting viruses that are reassortants between the B/Yamagata lineage and the B/Victoria lineage, so they have the hemagglutinin of the Yamagata lineage, the Y3 group, but they have the neuraminidase of the B/Victoria group, the V1A subgroup.

So these are still circulating. We see them in the U.S. There are several viruses here, from the U.S., and we see them in other parts of the world, also, in Asia, and Africa, and other regions, but they remain at a fairly low consistent level.

So just moving on to the hemagglutination inhibition test, that we use for influenza B viruses; again, the reference viruses. The antisera to the reference viruses are across the top. These are the homologous viruses, and their titers are shown in red on the diagonal. And highlighted in yellow, are

the results with the antisera raised to either a cell-propagated or an egg-propagated B/Phuket/3073 virus.

And you can see that all of the circulating viruses -- and we have viruses here, many of them from the U.S., we have some from Bangladesh, and some from Africa here. And again, the majority of these are Y3. We have some of these reassortant viruses in there, and even some of the Y2 viruses.

The vast majority or all of these viruses are actually reacting to the antisera to B/Phuket at titers that are within four-fold of the homologous titer. And that tells us that they are antigenically similar to the B/Phuket viruses.

So looking at this for antigenic cartography and this is just showing now -- this is color-coded. So this is all HI data from over this time period, and you can see that the more recent viruses from September 2015 onwards, are colored in yellow and the older viruses are colored in blue. And you can see that the more recent viruses, like the older viruses are still clustering very tightly near the B/Phuket reference viruses, both the cell and the egg-propagated viruses.

And this is the summary table of almost 600 viruses tested by all of the collaborating centers. And overall, 99 percent of these viruses were characterized as being

B/Phuket/3073/2013-like, so antigenically similar to the B/Phuket vaccine component. For the B/Victoria lineages, again these viruses are co-circulating with B/Yamagata, and in many cases are predominating now.

They all still belong to the V1A genetic subgroup, as does the B/Brisbane/60/2008 vaccine component for the B/Victoria lineage. These viruses that are circulating now have changes at residues 129, 117, and 146, compared with the older viruses, but they all still fall into the V1A lineage. And again, you can see very recent viruses from January and February, and there's really nothing new to report genetically with these viruses.

This is just, again the time series and you can see down here, these new groups that contain the 117V change. That really these are the predominating viruses right now, in the last several months.

For the neuraminidase, we do see this subgroup here that I mentioned in the previous slides. So this is the B/Yamagata lineage viruses that have the Yamagata HA, but they have the neuraminidase of the B/Victoria lineage. And otherwise, there's really nothing to really note with the neuraminidase.

So looking at the antigenic characterization of these

viruses by hemagglutination inhibition test, this is a CDC test, and you can see, so genetically these viruses are all V1A viruses. And shown highlighted in yellow on the left-hand side, is the antisera that are raised to the egg-propagated Brisbane/60 and its cell-grown counterpart. And you can see that the antisera raised to the cell-grown virus, covers very well all of the circulating viruses tested. The antisera raised to the egg-propagated, we do see some four-fold reductions, but that's still considered to be antigenically-like the B/Brisbane/60 virus.

And then, again, just showing the antigenic cartography, again, the majority of these viruses of the more recently circulating viruses shown in yellow, are clustering very closely to the B/Brisbane. I should have mentioned, on the previous slide, also -- I'm sorry to jump around a bit -- but I should have mentioned also, the reactivity with the Texas antisera shown here. It's not highlighted, but you can see, that antisera raised to the Texas/02 reference virus is also -- very well covers the circulating viruses. And Texas/02 is a candidate vaccine virus that is Brisbane/60-like, it's just a more recent B/Victoria V1A lineage virus.

And finally, of about 500 viruses that were

characterized from the B/Victoria lineage, by the different global laboratories, we see again that 96 percent of them are characterized as being B/Brisbane-like, similar to the B/Victoria lineage component of current vaccines, and only 4 percent showed reduced reactivity.

So in conclusion for the influenza B viruses, B/Victoria and B/Yamagata lineage viruses have co-circulated, but it's clear that B/Victoria lineage viruses are predominating in many countries, or where they're not yet predominating, they certainly have increased their proportions, as we have seen, for example, in the U.S. this season.

For the B/Yamagata lineage viruses, the vast majority of viruses belong to the genetic clade Y3, and only a very small number, now, belong to clade 2. And all the recently circulating viruses are well-inhibited by ferret antisera raised against either the egg or cell propagated B/Phuket/3073/2013 virus.

For the B/Victoria lineage, all the viruses have hemagglutinin genes that fall into the clade 1A. And again, recently circulating viruses are well-inhibited by ferret anti sera raised to either the Brisbane/60/2008 or the B/Texas/2/2013 viruses, representing the candidate vaccine viruses that are

available. And again, the majority of influenza B viruses that were tested were sensitive to neuraminidase inhibitors.

So as you've already seen from Ms. Cheung's presentation, based on the data that I've just shown you, last week the WHO group recommended the following composition for the 2016-2017 Northern Hemisphere season:

They recommended a California/7/2009-like virus for the H1N1/pdm09 component;

A/Hong Kong/4801/2015-like virus for the (H3N2) component;

For the trivalent vaccines, the B/Brisbane/60/2008-like virus representing the B/Victoria lineage;

For quadrivalent vaccines, the additional B component would be the B/Phuket/3073/2013 representing the B/Yamagata lineage.

And so I'd just finally, like to acknowledge all the people who contributed: these are the collaborating centers from Beijing, Melbourne, London, Tokyo, as well as Geneva staff; the Global Influenza Surveillance and System, which is comprised of about 143 national influenza centers in 113 countries, and we really couldn't do this work without the provision of viruses through this system, and it's just a fabulous effort every year;

Also, the University of Cambridge partners that provide important visualization of our data; the essential regulatory laboratories, as we'll hear from Dr. Zhiping Ye, later on, there's another component to the testing that we do, and he will provide the results of the serologic testing, looking at human sera;

We also have many U.S. partners; the APHL, as I mentioned earlier, our colleagues from DOD, who provide sequenced data for us and really enrich the data sets that we have, and also just a lot of people at CDC at the Collaborating Centers; and I'd just like to call out Dr. Xiyan Xu, who runs our virus reference team, who does most of this data analysis and collection, and she's here today; she's also the Deputy Director of our Collaborating Centre. Thank you.

DR. LYNFIELD: Questions?

QUESTIONS

UNIDENTIFIED PERSON: Yeah. Excuse me. I have a few here. The first one is, really, to go back to your point before, in terms of why the Brisbane, and not the Phuket in the trivalent. I mean in the U.S., it was, in the other data, it was 24 versus 17 percent. And here, globally it's 3 versus 2,

so still more predominant or I think that was on one of the -- it's okay, it's one of the early slides, I saw it. The other thing is, in the egg-grown Brisbane --

DR. LYNFIELD: Slide six.

DR. MOORE: In the egg-grown Brisbane, it's less of a match even than the Brisbane that's in the cartography, at least; it was on 52, or something like that, but you can go to this slide first.

DR. KATZ: Right. But, this is just what's reported to WHO. I think a better representation of what we're seeing, can really be seen with the sequence data, because the sequence data really demonstrates that the B/Victoria lineage is predominate, or has emerged to predominate in multiple regions. And if you'll recall, I don't know if we can go to that slide.

It was one of the last slides. It's probably around slide 50 or so. Go back. No it's more like 45. Keep going. There that one. Thanks.

So if we look by genetic groups, and this may not have been quite clear because of the labeling, but the orange represents the B/Victoria lineage, that is, the genetic grouping of the B/Victoria lineage that's now circulating. And you can see, again, the numbers are small for Oceania, for the September

period, but starting last July or August, in the middle of their season, they really saw this switch to the B/Victoria lineage.

It was also seen in this season in Europe, it's very clearly seen. There's a greater proportion of B/Victoria, although it's not the majority yet in Asia, and it's turning that way too, in the U.S. Last season, it was like three-to-one and it's expanding. So I take your point, but I think on the global level, I think we all think that -- and we know that the B/Yamagata and the B/Victoria lineage viruses, you know every few years switch backwards and forwards.

And we've certainly had the B/Yamagata lineage predominating globally for several seasons, so I think the experts felt that the B/Victoria's time was coming, and it was switching back toward B/Victoria.

Dr. MOORE: Okay. And a next question is going to the Hong Kong-like virus, but the term "like" in this particular case. Clearly, from the antigenic data and the other, that the Hong Kong itself is closer or better, particularly for the egg-grown virus, okay, than if you used a -- what -- at least the way I presume it, a "like" virus, such as Switzerland, or something else.

DR. KATZ: Actually, Switzerland is not a Hong

Hong/4801-like virus --

Dr. MOORE: Okay.

DR. KATZ: -- because it's 3C3A, and antigenically, we can discriminate those a little better.

DR. MOORE: So what would be included within the term, "like" in this particular case, as well? I thought that the -- some of these --

DR. KATZ: So for Hong Kong/4801, it includes cell-propagated viruses. And I didn't call out the actual names of all the viruses because I thought it might get a bit too confusing. But for example, the different centers use different cell-propagated viruses that are Hong Kong/4801-like, and we use a virus from Michigan.

The London group uses another Hong Kong virus, and so there's a series of viruses that when we test them antigenically, they meet the criteria, that we can call them "like." And so, because of the difficulties with (H3N2) viruses, we can't all be using Hong Kong/4801, especially for cell-propagated because of the challenges with the properties of these viruses in cell culture.

Dr. MOORE: One final question that I probably should last -- Gillian asked this, or something like this, but where

the NA is beginning to bind cells and other things that way, do you have any evidence or anything that anti NA antibodies then, become more effective in terms of the vaccines or anything else?

DR. KATZ: We don't have evidence for that. And really, we think that this is a cell culture phenomenon, because when we look at the original clinical samples, we don't see this heterogeneity in the neuraminidase. We see it when we culture the virus, primarily in MDCK cells.

And that was one reason, and I probably didn't give a full explanation of this either -- we've changed. We've moved to -- they're still Madin-Darby canine kidney cells, but they're a cell line called "SIAT" which have been engineered to express a little more of the receptor that human viruses like to bind to.

And when we use that cell line, we don't see so much of these changes in the neuraminidase, so we don't think that this is necessarily happening in a clinical sample or in a person. It's happening because we culture these viruses in order to try and characterize them antigenically. And so we've done these various manipulations including using the neuraminidase inhibitor to block that reactivity.

It's a very good question about the role of antibodies

to neuraminidase, in terms of protection, and whether vaccines should be more focused on that, but I think it's a topic for different day.

DR. LYNFIELD: Dr. Monto?

DR. MONTO: I think your question about neuraminidase antibodies, it is relevant because we have published with Jackie on the independent protection that neuraminidase does give in humans, based on some vaccine effectiveness studies that we've been doing. I think we have, as Jackie well knows, a semantic problem.

When we say, as in the previous presentation, that all of the viruses this year are A/Switzerland-like, when in fact they don't belong to the clade that A/Switzerland belongs to -- neither were they last year. All of the viruses we had, and we had a lot of failures, were 3C2A. And we know that everybody who failed, had high antibody titers, not only to the vaccine strain, which was A/Texas, but also to A/Switzerland.

This shows the real problem we have with A3 and 2, in terms of protection. Every time we do vaccine effectiveness studies, the best protection is against the B, that we worry so much about, in terms of trying to guess, which is going to be the predominant strain.

Next, is (H1N1) and even in well-matched years, it's (H3N2). And I think we really have issues to address with (H3N2), which -- and this is not the time, or the place for further discussion of those issues, but I think we have some real issues there.

Dr. ANDREWS: This is new for me, but I think I've been following it. I was really struck by the geographic differences for all of them, especially (H1N1) the most common, and I wonder what other countries, are making decisions right now, are they following the WHO? Are they crafting it for what they're seeing where they are?

And also, do we have regional differences? I mean, we do in the spread of the virus across the United States. Are there differences in the type that -- I get that you know virus types work, if you immunize someone against one type, it works to some extent, against others. And I get you have to grow it, which so takes me back, the troubles of growing a virus, but how do you take all those pieces, and craft it into a WHO recommendation and whether the United States should do the same thing?

DR. KATZ: Yeah. I think that's I guess, something that you guys will decide. But the Europeans will make a

decision in; I think it's another couple of weeks, the same with Japan. I'm not sure what other national authorities do, maybe our folks at CBER know that a little better, but they certainly take into account the WHO data.

It is very hard to predict from year to year, what's going to spread and what's going to circulate in a certain region. I mean there was Italy; in the middle of Europe was a standout, that it didn't have a lot of H1's. It had more H3's this year, apparently. So it's hard to predict, but I think you really need to go with the global picture.

Last year we saw in our USV network, we saw some interesting, very small, focused regional circulation of a particular genetic subgroup of (H3N2). And this season it's too early to tell, but at least we know that all the viruses in the U.S., are really, for the H3's, are 3C2A, the vast majority, and we know for the (H1N1)s, that the 6B1 genetic group is predominating.

DR. LYNFIELD: Jackie, I have two clarifying questions. One is, as long as we have slide 39 up, do you have a sense of the temporal change in Victoria versus Yamagata? When you were speaking, it sounded like, over time, Victoria came out, and so I just wanted to confirm that.

And also, in those areas where influenza has peaked, we've kind of had a late season. Can you comment specifically on that interaction with Victoria and Yamagata?

DR. KATZ: Yeah. So I think I can say, that it was very noticeable at the September WHO Vaccine Consultation, which was making recommendations for this year's southern hemisphere season. There really was a swing in southern hemisphere reporting of the B/Victoria lineage, so I would say it was starting to take off at that time. The B/Victoria lineage was starting to overtake the B/Yamagata lineage, in regions in the southern hemisphere. And then we've seen the same thing, quite dramatically in Europe, and it's increasing in proportions in North America, and in South America also, so I'd say, since sort of the middle of 2015, this has been happening.

With respect to seasonality, I guess -- I mean with respect to sort of the late season, we sometimes do see the B's emerge you know later in the season. We're clearly not done with our season yet, so it's hard to predict, but certainly with the numbers of viruses we're seeing in the U.S. at the moment. We're seeing more, as I said earlier, it was more, 75 percent or so Yamagata, 25 percent B/Victoria last season, and it seems that the B/Victoria is expanding at this time. Whether we'll

see further expansion of those numbers, as the season continues and tails off --

DR. LYNFIELD: It's hard to know.

DR. KATZ: -- it's hard to say.

DR. LYNFIELD: Right. And then if we could go to slide 52, for a moment? So I was just wondering if you could go through this slide again, because it looks like you know there's a bit of a difference between the egg-grown Brisbane and the cell-grown Brisbane. We don't have a cell for Texas in there, and I'm not sure which the Malaysia is, but I was wondering if you could just discuss this slide a little bit more.

DR. KATZ: Right. Okay. So the B/Malaysia is an older strain, it just is to demonstrate an earlier --

DR. LYNFIELD: Yes.

DR. KATZ: -- an earlier virus. So it's not really relevant. So in our hands, the B/Brisbane, any sera to B/Brisbane cell-propagated and egg-propagated, cover the circulating viruses quite well. We have seen that there is in some cases, a four-fold reduction in titer response, relative to Brisbane egg-grown.

In other centers, and I think this might be some

cumulative data of the different centers, so it's not just our data; in other centers, they see bigger differences with the B/Brisbane egg. And they are reporting their antigenic characterization based on antisera raised to Brisbane cell-propagated.

In different centers, there are unique -- each ferret antisera has a unique property, and sometimes, if antisera has a very high homologous titer, it has the appearance that there is antigenic difference, and that's another reason that we always have to you know take a step back, and look at the response relative to the cell propagated. And that's what we're doing here.

And so the distance with the B/Texas egg-propagated this year, was something that we saw in our laboratory. So I showed you on the HI table that the circulating viruses reacted very well with antisera to the Texas cell-propagated, but we had again, the situation where our antisera to the Texas egg-propagated virus had a very high homologous titer, so it made it look like viruses were not reacting as well. And that's probably why it looks like there's this distance in this particular antigenic cartography. But the viruses were actually from all laboratories, still showed good antigenic similarity

with Brisbane cell-propagated viruses, and that was across the board.

DR. LYNFIELD: Thank you.

DR. LYNFIELD: Any other clarifying questions?

(No response.)

DR. LYNFIELD: Okay. Then thank you very much, Dr. Katz.

It is time for our break. And can we give until 10:40 a.m.

DR. VIJH: That's up to you to say.

DR. LYNFIELD: Okay. Let's come back at 10:40 a.m.

BREAK

DR. LYNFIELD: … Dr. Cooper, who leads the Respiratory Pillar Activities, at the Division of Global Emerging Infection Surveillance, and Dr. Cooper will be speaking to us on the Department of Defense Vaccine Effectiveness report.

Great. Dr. Cooper.

DR. COOPER: Is this thing on? All right good.

DEPARTMENT OF DEFENSE VACCINE EFFECTIVENESS REPORT

DR. COOPER: Good morning. As mentioned, my name is Michael Cooper, and I am the pillar lead for the Respiratory

Surveillance Pillar at GEIS, which is, Global Emerging Infection Surveillance and Response Section of the Armed Forces Health Surveillance branch. As you've probably deduced, we are a DOD asset.

So today, I'll be presenting data on the 2015-2016 influenza season from our influenza surveillance network; included here, will be surveillance data from our partners in North America, Asia, Europe, and Egypt. In addition, surveillance data will also be presented on our recruit population within the United States.

I'll also be presenting a brief summary of the phylogenic analysis developed by our partners at the U.S. Air Force School of Air Space Medicine. These analyses were already covered in some detail by Dr. Katz in her briefing, so I will not spend a lot of time on that.

In addition, I'll be presenting free midyear vaccine effectiveness estimates, developed by our partners at the Naval Health Research Center, NHRC, in San Diego; the United States Air Force School of Aerospace Medicine, USAFSAM, and our Epi Analysis Section at the Armed Forces Health Surveillance Branch.

(Pause.)

My disclaimer.

(Pause.)

All right. So as I mentioned, GEIS has a fairly extensive respiratory disease surveillance program. We have about 400 locations in over 30 countries. We are dedicated to the surveillance of military populations, but not exclusively. We also have relationships with foreign ministries of health, foreign ministries of defense, and academic institutions, which enable us to do surveillance on local national populations, foreign local national populations.

We have extensive characterization capabilities, including sequencing, PCR, and culture, and we share our results with the CDC and WHO reference centers. During fiscal year 2015, our network collected and analyzed a little over 30,000 samples, and provided about 500 samples to the gene bank.

This gives you some idea of where we are in the world. The blue is where our partners are, and our sites. You'll see some red dots. Those red dots represent our embassy surveillance, which we are also involved with. And as you see, it's over 30 countries and 400 sites.

I'm going to give you a little background on the graphs here. Along the X axis, you will see the epi week. Along the left-hand Y axis, you will see a number of specimens.

The far right-hand side, you'll see the current influenza season, and on the left-hand side, you'll see last year's influenza season.

These data are for our military recruits. Military recruits are particularly vulnerable to respiratory diseases. Historically, up to 20 percent of recruit classes will be hospitalized for respiratory illnesses. Obviously, that plays a big role in progressing these individuals on to their next assignment. So it's obviously a very important issue within the military.

If you look at the right-hand side, you'll see that this season has been very mild, very mild. You'll see a mix of H1B and H3, but very low. What's more interesting, if you look back into June, you'll see an outbreak of influenza B, which highlights the need for year-round surveillance.

So again, these individuals are located at eight sites throughout the United States. These data come from military members and dependents located in the United States. Again, if you look at the right-hand side, you'll see our current flu situation, which is, again, is very mild compared to last year; again, there's a mix of H1, H3, and influenza B.

And here's our data for Europe. These are military

members and their dependents: family members; wives, husbands, children. And you see again very low levels, mostly H1, some flu B as well. We have probably about 150,000 individuals that come into this catchment area in Belgium, Germany, Italy, Turkey, and the United Kingdom. So it's pretty widespread, but again these surveillance data show that there's very little influenza in our military populations.

This data is specific to Egypt. You might wonder why do, we have slide specific to Egypt, where so far we've been talking about regions. Egypt is a longstanding partner with the DOD. We've had a laboratory there for over 50 years.

And aside from geopolitical reasons, Egypt is a very important because in recent history, they have had a large number of H5 cases reported, so we have a particular interest in Egypt. Again, this is a fairly heavy flu season; it represents a fairly heavy flu season. The vast majority of cases are H1, very little flu B, and this really stands out, I think.

This slide represents both local and national populations on their surveillance in Asia, and some of our military members. We have military presence in Korea, in Japan, in Guam, as well; other countries included in this, are the Philippines, Thailand, and Cambodia, and Bhutan. So it is a

mix, really, of U.S. military and local and national populations.

You can see, looking at the right hand side, this season is a mix of H1, H3, and B, a little bit -- compared to last year, a little bit stronger, a little bit heavier activity. And if recent history is any indication, they may peak in a week or two. Actually, over the past few years, we have seen that peak in March/April in this particular region.

So in summary, North American, Europe military members and dependents have experienced low flu activity so far. Positive samples have been a mix H3 and H1. Globally, a mix of H3 and H1, have been detected. In the DOD network, Egypt, so far, has experienced a relatively heavy season dominated by H1, and Asia has experienced a relatively heavy season with a mix of circulated viruses.

Now, as I mentioned, I'm not going to go into great detail regarding the phylogenic analyses. I would like to give you some idea as to where the DOD sequences came from. You can see, we submitted 196 sequences from a dozen countries and five continents.

I'd like to just hit up some of the highlights of the analysis: 66 percent of the total sequences were flu A,

influenza A; 71 percent of those were (H1N1); 29 percent of the flu As were (H3N2); 34 percent of the total sequences were influenza B and 70 percent of those were Yamagata, and the rest were Victoria; ninety-two influenza (H1N1) specimens were successfully sequenced from 32 sites in 11 countries, and these were collected between October 2015 and February 2016.

All 92 sequences classified as clade B, and 88 percent of the sequences shared the newly-emerging mutations: S162N and I216T. As for H3, 38 influenza specimens were successfully sequenced from 13 sites in 7 countries, collected between August 2015 and February 2016; 84 percent of the H3 specimens classified as clade 3C2A, containing the A/Hong Kong/4801/2014, and 16 percent classified as the clade 3C3A, containing the A/Switzerland/9715293/2013.

As I mentioned, to this point, the flu season has been relatively mild. Most regions covered by the DOD influenza surrounds network have seen very little activity. Overall, the number of cases available for these vaccine effectiveness analyses was down by over 90 percent from last year.

The midyear estimates are provided by our partners at USAFSAM, Naval Health Research Center, and the Armed Forces Health Surveillance Branch, Section Epi Analysis. Each was a

case-controlled study that used multi-variant logistic progression to estimate the vaccine effectiveness; two of the studies used control test negative method, that's the NHARC's study and the USAFSAM study.

Epidemiology and analysis at the Armed Forces Health Surveillance Branch used health controls. No analysis by flu type, due to the small number of cases, and each influenza infection were confirmed by PCR or viral culture.

Here, you see our testing criteria for ILI: if you have a fever greater than 100.5 F, or 38 degrees C, and a cough and/or sore throat; specimens should be collected within 72 hours of the onset of the symptoms.

And here is our USAFSAM. Thank you.

This is our USAFSAM estimate of vaccine effectiveness. They adjusted for -- well, first off, the population they used was health care beneficiaries, DOD health care beneficiaries, but not active duty. So these are again, spouses and children of active duty members.

The analysis is by a beneficiary group; children versus adults, and vaccine type; inactivated vaccine versus the live attenuated vaccine. In this analysis, test negative controls were used and the models adjusted for age, gender, and

region. Cases and controls were matched for week of illness, so this is a conditional logistic regression.

There were 119 cases, 294 controls: 15 percent of the cases and 37 percent of the controls were vaccinated; 53 percent of all cases were (H1N1) so that's the dominant subtype; only 9 percent of the influenza A's were (H3N2) so we're not going to be able to make comparisons between, or for each influenza subgroup; and 38 percent of the cases were influenza B.

Of those vaccinated, 26 percent were vaccinated with LAIV, the rest were vaccinated with the inactivated vaccine, so it really impacts on our sub-analysis; so no analysis by flu type and a limited analysis by vaccine type. Next slide, please.

Here's our age distribution for the USAFSAM analysis. You can see that about 50 percent of these individuals were under the age of 18; 24 percent between 18 and 49, and 26 percent were 50-plus. Next slide, please. All right.

The overall estimate for vaccine effectiveness, for all beneficiaries, that's adults and children combined, was statistically significant and protective. The vaccine effectiveness estimate for all beneficiaries, that's adults and children combined, vaccinated with the inactivated virus

vaccine, was statistically significant and protective. Next slide, please.

Here are our odds ratios. You can see for children at the top of the table. You'll see vaccine effectiveness is 75 percent with a confidence interval of 43 to 89 percent. And again, that's just comparing vaccinated to unvaccinated.

For adults, comparing vaccinated to unvaccinated, you have a vaccine effectiveness of 64 percent. And when you try to split out the inactivated versus the LAIV, you'll see that the inactivated vaccine is quite high at 83 percent, and statistically significant. The LAIV, you have very small numbers, so the statistical power didn't make that comparison, not very good. Next slide, please.

Next up, is our NHRC case control analysis. Next slide please. Yep. Thank you. The population used in this analysis, were civilians only. Some of them were DOD dependents residing in Southern California or Illinois, and would have been seen at outpatient clinics.

The civilians in this analysis, were completely unassociated with the DOD, are individuals who sought healthcare at the U.S./Mexico border. So again, these are all civilians; part, are dependents, and these analyses adjusted for age, study

population, military dependents versus U.S./Mexico border civilians, and month of illness. And there are 106 cases and these were confirmed by PCR or viral culture.

Two hundred and sixty-seven controls and these are again test negative controls. And you have, about 20 percent of your cases were vaccinated and 38 percent of your controls; 58 percent of cases were (H1N3) and 25 percent were flu B with only 15 percent (H1N1).

So you can see how NHRC's data and analyses are almost a mirror image of USAFSAM's. So it gives us an opportunity to look at H3 or H1, but not together, not simultaneously, in a logistic progression. Approximately 90 percent of the vaccinated cases and controls were vaccinated with the inactivated vaccine. So we're not seeing a lot of LAIV use in our study populations.

Here's your age distribution: You can see 77 percent are below the age of eighteen; about 20 percent 18 to 64, and 3 percent 65 and up. Overall, the adjusted VE was moderately protective and statistically significant. For children, the VE was moderately protective and statistically significant. The adjusted VE for (H3N2) infection specifically, was moderately protective and statistically significant.

And here are the odds ratios: You can see the overall, 48 percent; looking at H3, specifically, 66 percent vaccine effectiveness, and children 18 and below, H3 only, you see an odds ratio or I should say vaccine effectiveness of 66 percent.

The Armed Forces Health Surveillance Branch's analysis used the health control, and the population analyzed here was active component service members, and Navy, Air Force, Marines, and Army. And these are both individuals residing within the United States and outside the United States. We had 183 lab-confirmed cases; last year, we had about 2,000 for this analysis, to give you some idea.

Health controls were used. The medical encounters, individuals who had medical encounters for injuries or mental health conditions, with no ILI reported in any encounter, and no medical encounters for influenza during the flu season. These individual cases and controls were matched by sex, age, date, and date of encounter and location.

In addition, the models adjusted for a five-year vaccination status, meaning that if an individual had any flu vaccination in the previous five years, they would be a yes; so for any of it, whether it be five or just one. Overall and

vaccine type VE were calculated.

In addition, going back to the five-year vaccination status, that's proven to be a very important variable in our models. About 90 percent of our cases and controls indicate a vaccination in the previous five years. Here are our age groups.

And I apologize. In your handout, I believe the last age group was left off, but you can see the lion's share of our cases, are between 30 and 39. Keep in mind that the U.S. military, these are active duty individuals. The U.S. military tends to be considerably younger and healthier than the population at large.

So 84 percent of the cases were vaccinated and 87 percent of the controls; this obviously has a substantial impact on statistical power; 90 percent of cases had prior flu vaccine in the previous five years; of those vaccinated, 59 percent were inactivated vaccine and 41 percent were vaccinated with the LAIV.

Adjusted VE of 24 percent was calculated for overall, and that was not statistically significant; adjusted VE of 16 percent for those who received the inactivated vaccine was calculated, and that was not statistically significant; and

adjusted VE of 39 percent was calculated for those who received the LAIV; and again, not statistically significant.

Here are our odds ratios. So when looking at active duty, there was no discernible vaccine effectiveness; however, looking at the civilian populations, it was moderate to strong.

So summarizing the results: Regarding USAFSAM and NHRC vaccine analysis, overall VE, all flu and vaccination types were statistically significant and moderately protective; the vaccine effectiveness for inactivated vaccine, specifically, was statistically significant and moderately to highly protective.

The USAFSAM and NHR C analysis indicate that the inactivated vaccine prevented between 64 and 83 percent of medically-attended influenza cases. Regarding the Armed Forces Health Surveillance Branch's analysis, none of the findings were statistically significant, and there are substantial limitations to our work here.

Subjects were sick enough to seek medical attention, so we can't really comment on the impact for the less severe cases. Due to relatively small numbers of cases, the vaccine effectiveness by flu subtypes, or vaccine type could not be estimated. For the USAFSAM and NHRC analysis, over 80 percent of vaccinated cases and controls were vaccinated with the IIV,

so you can't compare VE by vaccine subtype. And the numbers were too small to adequately evaluate the LAIV vaccine.

Regarding the Armed Forces Health Surveillance Branch analysis, the active duty military population is highly immunized; generally speaking, it's over 90 percent, although, this year it's a little bit lower at this point, due to some delays in getting the vaccine out. This could have a negative impact on the VE, potential methodological issues.

Keep in mind, if 87 percent of your controls are vaccinated, your number requirement for statistical power purposes is very high, and that is the case in our situation. We have -- 87 percent of our controls were vaccinated. So you have potential methodological issues, potential biological effects, such as it's an attenuated immune response, which was mentioned a little bit earlier today, with repeated exposures.

Also the military population is younger and healthier, so we can't really comment on vaccine impact in older, high-risk populations. And again, the small number of cases really limited the analysis.

I'd like to acknowledge our partners, too many to mention, but they had a lot of contributions to this work, and we appreciate their efforts. And I'll be happy to take any

questions.

DR. LYNFIELD: Thank you very much, Captain Cooper. Are there some clarifying questions?

QUESTIONS

Yes, Dr. Monto?

DR. MONTO: I think the results from the NHRC analysis are particularly interesting. First of all, because you got a fair number of (H3N2)'s and one of the sites was Illinois, and the other was San Diego?

DR. COOPER: San Diego, yes. And I checked into this, it's very -- less than 5 percent of the cases came from Illinois.

DR. MONTO: Okay. All right.

DR. COOPER: So it's --

DR. MONTO: Because in the Midwest, it's been nearly all pandemic/H1N1 --

DR. COOPER: Right.

DR. MONTO: -- with a smattering of B's from the start of the year. Obviously, you don't know what clade this virus belonged to, but the estimates are very high for (H3N2). Do you have any information about past vaccination of these individuals?

DR. COOPER: No. These --

DR. MONTO: Not yet.

DR. COOPER: Well, exactly. These individuals, we don't have access to their -- currently, to their medical files.

DR. MONTO: Um-hm.

DR. COOPER: So there's no information on previous vaccine.

DR. MONTO: Um-hm. Thank you.

DR. LYNFIELD: So Captain Cooper, I wonder if I might ask you a question.

DR. COOPER: Sure.

DR. LYNFIELD: You, I believe, you had mentioned that there was some characterization of the B viruses, with 70 percent being of the Yamagata lineage and 3 percent Victoria. I'm wondering if you can comment. Were these viruses that were from around the world or were they from a particular region?

And what proportion of the -- what is the total number of viruses that were characterized, compared with the total number that you have reported?

DR. COOPER: Well, you've got to remember these analyses are just a subset of what was already presented.

DR. LYNFIELD: Yeah.

DR. COOPER: So I can tell you that 196 sequences came from our network into the CDC analysis.

DR. LYNFIELD: Okay.

DR. COOPER: But the total number of viruses, I'm afraid I don't have information on.

DR. LYNFIELD: Okay. And were these from throughout your surveillance system, or were they from a particular area?

DR. COOPER: They're from throughout the surveillance system, but I don't have information as to where exactly the B's came from.

DR. LYNFIELD: Okay.

DR. COOPER: Yep.

DR. LYNFIELD: Thank you very much.

Any other questions?

(No response.)

DR. LYNFIELD: Okay. Thank you, Dr. Cooper. Okay.

And I would like to invite our next speaker, Dr. Zhiping Ye, from the FDA, and Dr. Ye is a senior investigator at the Division of Viral Products; Office of Vaccines Research and Review, at CBER/FDA, and he will be speaking to us on vaccine responses.

DR. YE: Thank you very much.

VACCINE RESPONSES

DR. YE: In her presentation, Dr. Katz presented an antigenic characterization of the circulating virus using ferret model. In this presentation, I will present the antigenic characteristics of a circulating virus using human cell. And those serum panels usually come from the clinical trial, if the trivalent or quadrivalent vaccine contained the current vaccine compositions.

And different from the ferret study, in human, we do not have serum from the clinical trial contain the proposed antigens such as Hong Kong/4801. So in my presentation, I'm only looking at the antigenic relationships of a circulating virus, compared with reference virus, as usually it's the virus that are used for production of the vaccine.

And also, the sera panel usually come from the clinical trial, contains the current vaccines. And usually the panels contain 24 individual serums. So for a trivalent vaccine, we have five panels, and for a quadrivalent vaccine, we collected seven cell panels, and those panels were distributed to the six laboratories from WHO, CDC, ERL's.

And then the method is exactly the same as the method,

which was mentioned by Dr. Katz, and we use HI assay, and also we use microneutralization assays, and to increase the sensitivity of the assay, the serum panel is pre-screened to eliminate the low antibody. The samples contain a low antibody titer to increase the sensitivity. So my presentation is just going to focus on, to compare the antibody titer against the circulating virus, versus the reference virus.

And we wanted to look at, whether the serum sample come from a clinical trial cannot tell the difference between a circulating virus and the reference virus. And if the relationship of the circulating virus is very similar to the reference virus, that means the antibody can cover pretty well, to the circulating virus. And if we see the difference that means the antigen similarly, the antibody may not cover very well, to the circulating virus and that's indicate that this strain probably will be updated. And the assays, we don't have the sera from the clinical trial that contain the proposed antigen, so only see the one way.

This slide shows the serum panels from trivalent vaccine. I just wanted to point it to you that the vaccine contains (H1N1). In this case, A/Christchurch is the California-like virus.

And in the first cell panels, we can see this is from Australia. It contain the A/Christchurch for (H1N1); for (H3N2) it's Switzerland and for B -- is a B/Phuket. And for China, they use a different (H3N2), but it is still this Switzerland-like virus.

And this slide shows the quadrivalent, and basically it's similar to the trivalent. The only thing that's different is it contained the B/Brisbane-like antigens in the clinical trial. Okay. Now, I want to focus on (H1N1) virus.

And just to refresh your memory, the virus we selected are from the start. So here is, as Dr. Katz mentioned, the (H1N1) virus, the majority of them are clades 6B1 and 6B2. And what we did is we choose the virus from those clades.

Okay. This slide just show to you that -- these our reference antigens, either California or California-like; either California, itself, or A/Christchurch. And for the representative virus, which unlike the ferret study, for humans, they're for human serology study we only can include a few antigens. So we're not select all of them, just a few, to study the antigenic differences.

And you can see here, we include 6B1. And also we tried to cover the different geographic, from Michigan, from

Asia, and that also contained the 6B2 viruses. And then also, we want to include some of the non 6B1 or 6B2 virus.

Okay. This slide shows the summary HI titers from six lab, and then we look the antigenic, the differences of the circulating viruses compared with the reference virus. The red bar shows the summary HI, relative HI titers from adults. Then the blue one, are from the old adults. Then the green one, are from children.

By the way, the children come from the age 6 months to 3 years old, and for some panels, from the 6 to 2 years, and some panel from 3 years, and 3 years comes from China. And then for children, they immunize either one dose or two doses, based upon the previous immunization history.

And here you can see that what we will try to compare the circulating virus with reference virus. Since the vaccine produced from the vaccine viruses are from egg, so here we wanted to compare the antibody against eight propagated (H1N1) virus.

And you can see here, that is the reference virus. And then now, we look at the relative GMT titer compared to this reference virus. First of all, you can see that the second column, are the antibody against cell-propagated (H1N1) virus.

And you can see here, this indicated that the antibody against egg-propagated virus, different from cell-propagated virus, and it's in the singular virus, but propagating a different host and that indicate that maybe some of the antibody recognize egg, did not recognize cell-based viruses.

And then the rest of them, I just wanted to show to you our color-coded too. And the blue one 6B1 virus, I just wanted you to see the difference. And then the green one, are the 6B2 viruses.

We look at this, the relative to the compared to. Usually we use a 50 percent, just to see if a -- I think some study shows that if the antibody, the relative antibody above the 50 percent, it most likely they simulate a good, or match well to the reference virus. Anyway, so we -- just look at the overall pattern.

And here, we include either egg isolates or cell isolates. And overall you can see that either adult or children, it's react relatively well to the 6B1 and 6B2 viruses. However, when you -- next slide shows that when you compare the antibody, against the cell-propagated virus, you can see the different pattern.

Here you can see that when we use a cell-based virus

as a comparative, as a reference, you can see that the egg-based virus have very -- again, you can see this -- they have a very high antibody titer, compared with the cell-propagated virus. And because you compare now is different, and the rest of the virus you can see that when you compare with the cell-propagated virus, the circulating virus are covered pretty well.

So this data shows that the majority of the representative (H1N1) virus tested, react well with the human serum collected from an individual who received the current vaccine. And however some of the recent viruses, like 6B1 and 6B2 reacted poorly, but the majority react well.

Here is the point that we -- here is, just to address your attention that we probably needed to follow up those viruses, and see how those viruses evolved antigenically.

Now, we move our (H3N2). Again, we choose the viruses contained 3C2A and 3C3A, but a majority is the 3C2A. And here you can see that the majority of the virus are from 3C2A and some of 3C3A, or 3C3B. And the underlying virus was used in microneutralization assay.

As Dr. Katz mentioned, some of the virus does not aggregate red blood cells, so you cannot do that in HI assay. However, we include those viruses in microneutralization assay.

Again, it's similar to the (H1N1) in here, we compare the cell-propagated virus. And again, the blue bar indicating the viruses belong to 3C2A, and the red represent the 3C3A viruses. And as you can see here that the majority of the virus reacted poorly, compared with the cell-propagated reference virus.

Then regardless, cell or egg, so this -- yeah that is -- okay, I think it's -- and also, similar to (H1N1), you can see that when we compare with cell-propagated (H1N1), which is a Switzerland virus, the Switzerland cell-propagated virus react relatively low, compared with egg-propagated virus. And also, you can see here that the majority of these viruses reacted poorly, compared with the egg-propagated virus.

Now, if compared with cell-propagated virus, a cell-propagated Switzerland, which is the current vaccine virus, then you can see that the majority of the circulating virus that we choose for this study, reacted well compared with those from the data using egg-propagated virus. So that since we do not have the serum from, like the Hong Kong/4801 virus, so we cannot see how the same reacted to the circulating virus.

Okay. This slide show that the -- if we switch to Hong Kong/4801 virus, could -- may increase the coverage of the

vaccine, but however, we do not have the serum against this virus, so this data only suggested that from the ferret study. And again, the viruses were also used in microneutralization assay. And here the similar pattern, but in a different degrees that -- this one shows the egg-propagated virus.

You can see that the majority of the virus is not covered well with this -- with the sera from these clinical trial contain the Switzerland-like virus. However, when you compare with the cell-propagated virus, now you can see the coverage it's much better.

So the bottom line for the (H3N2) viruses, compared to the HI titer against cell-propagated Switzerland vaccine virus, the HI titer of the antibody against some of the represented virus, was significantly reduced. When measured against a cell-propagated virus, the GMT titer is higher, and also using microneutralization assay, it confirm its finding.

Now, move on B viruses. This slide shows both Victoria and Yamagata lineage virus, and as you can see here, the B/Phuket is Yamagata reference virus, and B/Brisbane/60 is the Victoria-like virus. And here you see that the green color-coded are the viruses from Yamagata lineages, and the brown one represents the viruses from the Victoria lineage.

Here, I want you to pay attention that's because this is -- these all come from the trivalent vaccine. And now, in this study, we include the virus, the circulating virus from Yamagata lineage and from Victoria lineage.

And without looking hard, you can see that Yamagata virus, circulating virus, react relatively well to the reference antigen, where the circulating virus, from Victoria lineage, you can see this, it covered poorly, indicating that the vaccine contained Phuket covered well to the virus, similar to the Yamagata virus, because it does not contain antigen against the Victoria, then it's Victoria virus does not cover well, and very clear in this study.

This slide just shows conversely, this slide show the reactivity using quadrivalent vaccine. And in this study, we didn't include Yamagata virus. We just include the Victoria virus that did not cover well in the previous slide.

And you can see here, majority of the virus covered pretty well, using the -- compared with the even egg-propagated Brisbane/60 virus. And for a B virus, a GMT of antibodies against the majority of a recent B/Yamagata lineage virus was similar to the HI titer, against Phuket vaccine virus.

As expected, the GMT titer to the Victoria lineage

virus was reduced in the panels that not contain this antigen. Where the antigen -- where the panels contain both, covered both well, to either Victoria or Yamagata viruses.

To wrap it up, the majority of the recent representative viruses reacted well with the human sera collected from an individual who received the vaccine contained California/07-like antigens. Even though there are some viruses -- some of the viruses not react well, but it does not change the conclusion.

And for (H3N2) virus, GMT titer against (H3N2) viruses, significantly reduced compared to the HI titer against egg-propagated virus, which is Switzerland-like virus, but less so when compared to the egg-propagated virus. And for B viruses, it's pretty clear if the vaccine does not contain the next -- the (inaudible) B, and does not cover well for both lineages. Thank you.

DR. LYNFIELD: Thank you very much, Dr. Ye.

Does anyone have any clarifying questions? Dr. Monto?

QUESTIONS

DR. MONTO: I'm a little surprised, given the fact that you gave egg-adapted virus in the vaccine that the response

is better to cell-culture-grown antigens.

DR. YE: I don't think the data shows the -- could you point out exactly, which virus --

DR. MONTO: Well, I'm talking about the (H3N2). The summary, is that the "measured against cell-cultured propagated virus, GMT of antibodies against recent viruses was relatively higher." Is that -- maybe I don't understand, which is -- are you comparing in the HI test, with antigens that are cell-culture-propagated versus egg-propagated?

DR. YE: I think when you compare with cell-propagated virus, we are referring to the circulating virus, and the virus not covered so well. However, when you compare with a cell-propagated virus, because now you normalize the antibody, against a cell-propagated virus, because cell-propagated virus compared with an egg-propagated virus, have relatively lower HI titers.

Now, because the HI titers lower, now you compare with the -- the circulating virus with the cell one. Now you see that virus covered well, when you compare with the cell-propagated virus. Indicate that if you choose the virus, the (H3N2) virus, that stimulant antibody covered relatively well, compared with the cell-propagated virus. That virus may be

better to be included in the vaccine, such as Hong Kong for the 4801 virus.

Did I answer your question?

DR. MONTO: In part.

DR. YE: Okay. We can discuss later.

DR. MONTO: Let's take this offline.

DR. YE: Okay. Thank you.

DR. LYNFIELD: Any other clarifying questions?

DR. KATZ: Yes, I have one. Are these individual sera or are they pooled?

DR. YE: These are the individual sera. As I said, each panel contains 24 to 30 sera samples, and this study, a summary of this individual one, and also include -- we started it in different labs.

And then here, I showed -- acknowledge that the data from what I presented, I'll summarize it from different, WHO and ERL laboratories. And also I think for those who provided the same sample for the study, a human sera sample now, is a very (inaudible) especially when used for microneutralization assay, we use a relatively large quantity.

DR. KATZ: Thank you.

DR. LYNFIELD: Thank you very much, Dr. Ye.

Now, I would like to ask Dr. Manju Joshi to come to the podium. And Dr. Joshi is the lead biologist at the Division of Biological Standards and Quality Control, the Office of Compliance and Biologics Quality at CBER/FDA. And she will be speaking to us on candidate vaccine strains and potency reagents. Dr. Joshi.

DR. JOSHI: I don't need this.

CANDIDATE VACCINE STRAINS AND POTENCY REAGENTS

DR. JOSHI: Hello everybody. I work in Division of Biological Standards and Quality Control, in the Office of Compliance and Biological Quality at CBER. "DBSQC" as we abbreviate our division. It's too long a name.

In collaboration with other essential regulatory laboratories, participate in generation and calibration of reagents required for testing of influenza vaccine. Our division also manages and provides these reagents to all U.S. licensed manufacturers.

In next 10 to 12 minutes, I will give you an update on the candidate vaccine strains, and go over our division's goal towards preparing and supplying influenza vaccine testing reagents for 2016-2017 season.

In my talk, I will go over currently-used vaccine strains, and also the WHO recommendation for 2016-2017 seasonal vaccines, both the trivalent and quadrivalent. I'll give you an update on the available reagents for each of the strains, as we have now.

And lastly, I'll make some general comments about use of SRID reagents, and which I will tell, which is more for the audience, the users of the reagent, not so much for the Committee, as such.

Coming to the (H1N1) strain, for influenza A, (H1N1) type the current vaccine strain was the A/California/7/2009-like virus. A number of reassortants have been used in the manufacture of vaccine last season. This included the X179A and X181 reassortants, even the NIB-74 and 74-xp reassortants for A/Christchurch, which is a California-like, have been used in vaccine.

In addition, B/Brisbane/10/2010, which is also a A/California/7-like virus, was used in vaccines. Most of us in this audience know that WHO and they have been repeated by all the previous speakers that the WHO has recommended there'd be no change for (H1N1) strain for upcoming influenza season, and A/California-like virus remains as the (H1N1) component.

I've listed here, and I'm not going to go over the names here, all the various candidate vaccine viruses which are A/California-like. I just want to remind A/California/7/pdm09-like virus has also been recommended for 2016 southern hemisphere campaign. We all understand that inclusion of WHO-proposed strains in the vaccine is based on approval by the Committee today. To stop, and for now, just let's look at the reagents that are currently available for testing the strain.

For homologous reference antigen for reassortant X179A and X181 are available from CBER. In past, some of the vaccine manufacturers have used a reference antigen from other ERL's such as egg-derived antigen for X181 from TGA, NIB-74 from NIBSC, as well as cell-derived reference antigen for A/Brisbane/10 from NIBSC.

As far as available antisera are concerned, three different antisera lots are available from CBER for testing of (H1N1) component. We'd like to point out that we are getting low on the two lots, 1404 and 1405 that most of the manufacturers had used last season, but we have already prepared a new lot for testing. And in addition, we are in process of making additional lots in coming weeks.

At this point, again, I would like to remind the users

of the reagent that some manufacturers may choose to use reagents prepared by other ERL's. CBER will authorize use of those reagents on a case by case basis. We would like to know ahead of time which reagent each of the manufacturers will be using, and this is very important for us because this will help us in planning for all the vaccine lot release activities.

Coming to the (H3N2) strain for 2015-2016 season, the recommended strain was A/Switzerland/9715293/2013-like virus. The NIB-88 reassortant of A/Switzerland, and IVR-175 reassortant of A/South Australia were used for vaccine manufacturing. Wild type A/South Australia was used in cell-derived vaccine.

Last year, the reagents were made available by ERL's. NIB-88 reagent for egg-derived vaccine prepared using NIB-88 reassortants, CBER, and NIBSC, and NIID had provided the reagents for IBR-75 egg-derived vaccines. TGA had prepared and supplied the reagents, and as far as A/South Australia cell-based products were concerned, reagents were provided both by CBER and NIBSC.

The WHO has recommended a change of the strain, and the recommendation is for A/Hong Kong/4801/2014-like virus. The various candidate vaccine viruses in this group are listed here. Let me just remind everybody, this has been recommended as the

(H3N2) strain for 2016 southern hemisphere campaign as well.

CBER is in process of getting reagents ready for A/Hong Kong, if the strain gets selected by the Committee, and we are anticipating the target availability date for this reagent to be late May into early June.

I just want to remind that the reagent for X-263B, the reassortant of A/Hong Kong, is available from NIBSC. And similarly, for X-257A reassortant of A/New Caledonia, which is A/Hong Kong-like strain, are also available from TGA and NIBSC. Again, I want to reiterate that CBER will authorize the use of reagents from other ERL's on a case by case basis. Please consult with DBSQC prior to using reagents from other ERL's.

Coming to the influenza B; for 2015-2016 season for trivalent vaccine, the recommendation was to use the B/Phuket-like virus from B/Yamagata lineage. Wild type B/Phuket and Wild type B/Utah/09/2014, which is a Phuket-like virus, were used in vaccine preparation last season. For egg-based product using B/Phuket, reagents were prepared by CBER, NIBSC, and TGA. And for cell-based product prepared using B/Utah, both CBER and NIBSC had prepared reagents.

WHO has recommended a change for B strain in a trivalent vaccine; for 2016-2017 influenza season, WHO

recommends that the trivalent vaccine contain a B/Brisbane/60-like virus from B/Victoria lineage. The various candidate vaccine viruses for these groups are, again, listed here on the slide. Please note that the B/Brisbane/60 was included as a second B strain for quadrivalent vaccine in the previous season.

Again, this has also been recommended as the B component for the southern hemisphere vaccine. If the strain is selected by the Committee, here is CBER status of the reagent currently: B/Brisbane/60 reference antigen for both egg and cell-derived product are available from CBER.

If manufacturers do choose to use B strain, other than B/Brisbane/60, CBER will vote to generate homologous reference antigen standard, and the target availability will be around May/June 2016. I'm sorry for the typo. It's 2016.

Coming down to availability of the antisera, which is always needed, the inventory for antisera lots serum, which were supplied last year, and most of the manufacturers have used, this is getting low. We have already prepared two new lots of antiserum, and they are available.

And once again, I think it's becoming too repetitive to say that, please consult with us before start to using reagents from other ERL's.

We all know that the quadrivalent vaccines are supposed to contain an additional B strain from alternate B lineage, referred to as second B strain. During 2015-2016 season, WHO had recommended that the second B strain for quadrivalent vaccine be B/Brisbane/60-like virus from B/Victoria lineage. This year WHO has recommended a change for the second B strain and quadrivalent vaccine.

For 2016-2017 influenza season WHO recommends that the quadrivalent vaccine contain a B/Phuket-like virus from B/Yamagata lineage. Again, here's the list of various B/Phuket-like candidate vaccine viruses on the slide. Just to come back, this strain was recommended as a B strain for both trivalent and quadrivalent last year.

So basically, it is, we had this as a main B up there this year, it is only for quadrivalent. And again, to remind this has also been, similar recommendation has been made for 2016 southern hemisphere campaign. Looking at the reagents that are available for the second B strain, the reagents for egg-derived B/Phuket is available from CBER. Similar reagents for B/Phuket were provided last year, even by NIBSC and TGA.

In addition, NIBSC had last year prepared reagents for B/Brisbane/9/2014, which is a B/Phuket-like virus, and they had

prepared it for the last season, and they have it. For cell-derived product, we do have B/Utah reference antigen for B/Utah prepared by CBER. And similar reagent is also available from NIBSC.

Coming to the different antiserum lots that are available from CBER, if the strain is selected and it needs to be used, we have lots 1507 and 1508, which were prepared last year. As we are getting low on our inventory for those lots, we have already prepared two new lots of antisera. Again, the standard reminder, please consult with us for any of the reagent use from any other ERL.

Now lastly, I would like to make some comments, which are more relevant, again, to the users of the SRID reagents. CBER-authorized reagent should be used to test potency of vaccine marketed in U.S. CBER collaborates with other ERL's in calibration of reagents, and can authorize the use of those reagents.

Please remember that users have to obtain this reagent directly from the ERL's. To avoid discrepancies, CBER recommends that to use the reference antigen and reference antisera from same source, and not mix and match. Again, we do recommend that the same reagent be it's desirable to use the

same reagents for your monovalent vaccine for the formulations and any other follow-up studies.

One more additional reminder is, especially for those who are getting into making new products, is, please discuss with CBER about use of reagents in early phase. Manufacturers and CBER can work together, to ensure that required reagents are available to test new products.

And lastly, I would like to point out that if you have any inquiries regarding CBER, our reference standards, and reagent availability, and shipping, please contact CBER Standards at the email address provided. And also, do please, do notify us if you have any problem with the reagents, and we will be happy to discuss.

Lastly, in closing, I want to emphasis that we at CBER are committed to make every effort to ensure that reagents appropriate for all strains elected are made available in timely manner. We believe that making the influenza vaccine available in timely manner, and ensuring vaccine consistency is a responsibility shared by all of us here, and we work together as a team to achieve this goal. Thank you. I will take any questions.

DR. LYNFIELD: Thank you very much, Dr. Joshi.

Any clarifying questions?

(No response.)

DR. LYNFIELD: Okay. Thank you.

DR. JOSHI: Thank you.

DR. LYNFIELD: We are running a little bit late, but I think we would like to have the next talk prior to lunch, and so I'd like to invite Dr. Matthew Downham to the podium, to speak from the manufacturers' perspective. Dr. Downham is the Associate Director of Biopharmaceutical Development Research and Development at AstraZeneca/MedImmune.

DR. DOWNHAM: Okay. Good morning, or maybe good afternoon everybody.

COMMENTS FROM MANUFACTURERS

DR. DOWNHAM: I'd like to firstly, thank the Committee, on behalf of the flu manufacturing community, for this opportunity to present their influenza perspective, the industry perspective. As indicated on the slide, this is presented, together, from Sanofi Pasteur sequeres (ph) GSK Protein Sciences. And the company I work for, of course, AstraZeneca/MedImmune.

So firstly, I'd like to start with where Sam Lee took

us last year at this time, and that is to reference the complexity and intricate detail that's required for annual influenza vaccine U.S. supply. And particularly also the timeline, drawing attention to the strain selection decisions that come at the end of February, and the limited timescale taking approximately 6 months through to delivery and supply of shipments.

So the point to make here is that any sort of delay in the strain selection will impact vaccine distribution schedules and that's indicated by the animation that we have on the slide here. By clicking the button, you can see what happens if we shift the strain selection even by a small period of time, to the mid-to-late end of March. Okay.

So if you look at the U.S. influenza vaccine distribution from 1980 through to the modern day, 2016, it's quite an impressive statistic. If you look at the figure on the left-hand side, 1980 to 2014, there's been a progressive increase in the number of vaccines supplied to the U.S. markets. In fact, the note's rather small, but up there, (inaudible) was 146,000,000/147,000,000 doses per year.

If you look at the figure on the right-hand side, you can see the projection of how those supplies are delivered, at

least for the 2014-2015 season, with the first deliveries implemented in September of that year, and then hitting the approximate plateau, around 140,000,000 doses in about towards the end of November of that same year. So, vaccine supply obviously requires a well-matched strain, sufficient quantities, and timely pre-season delivery, obviously all very important factors.

And by checking the CDC website, I did prior to submitting the slides, to date, as of the 19th of February, 2016, there's 146,000,000 doses, slightly over, distributed. And those distributions and supply were initiated in early September 2016. So if we think again, back to the, what if you delay or what if we delay strain selection, how might that impact things.

Well, in the 2014-2015 season strain selection was implemented, not at the end of February; however, if we did it at the end of March, the strain selection would have delayed the initial dose supply, to approximately October 2014, and with a commensurate meeting of the peak, not in late November 2014, but actually late December, so quite a substantial shift.

This slide just briefly indicates to you how we are faring for the current season. It indicates the influenza

strains that have been evaluated thus far for the northern hemisphere. And we've heard already today, from several presenters on the strains that were recommended last week, by the WHO for the northern hemisphere.

What you can see is just the range, a number of strains that have been evaluated by industry, and by other organizations; for example, Doris Bucher's lab in New York Medical College. And Doris is here today, as well.

What I'd like to also draw your attention to, is the recent addition of the 6B1 and 6B2 strains, into the (H1N1) portfolio, as a result of the strains that are emerging that Dr. Katz demonstrated for us a little earlier today. So if you think about these 6B strains that are emerging, manufacturers have had some discussions regarding these, in terms of what might be the impact for supply for the current season, and there are some concerns regarding the late emerging (H1N1) genetic subgroups.

Firstly, the (H1N1) viruses are typically a lower yielding strain than the (H3N2) viruses, and so require longer manufacturing campaigns to fulfill stock requirements. Currently, as far as I'm aware, there are no new representative viruses or CVV's confirmed, so that's Canada Vaccine Viruses

confirmed. To confirm, we would need, not just antigenicity, data, and the selected candidate, obviously, but high growth reassortants identified and also obviously, a potency assay available as well.

As was mentioned a little earlier, manufacturers do actually begin production of their flu vaccine candidates at risk. And as is often the way, significant quantities of (H1N1) amounts of 2016 have already been stockpiled. And delaying further will impact timing and quantity of supply, accordingly.

So if we go back to the Visio gram that I showed a little earlier, if we impact that scenario onto the current status, a two to three week delay of (H1N1) strain selection now, today, would delay influenza vaccine supply by approximately four months.

So if we assume a two to three week delay to identify representative viruses and confirm those, an additional three-plus weeks to prepare the reassortants, and an additional twelve-plus weeks to prepare potency assay reagents that shifts the whole picture to the right-hand side, as you can see, and obviously delays quite significantly, vaccine supply to the market.

Moving on to how industry engages with multiple

stakeholders. So we don't just discuss amongst ourselves, we engage very much with key stakeholders globally, with the WHO, and also with HHS just to improve the season influenza vaccine supply. And this Visio just gives you an idea of how many meetings and what we've talked about, between today, the VRBPAC meeting today, and last year's VRBPAC meeting, which was actually on the fourth of March 2015.

In light blue, you can see the seasonal flu review meetings. And these are the meetings that the likes of Dr. Katz, etc., present from the WHO on the seasonal circulating surveillance, from the GISRS that was mentioned a little earlier, and (inaudible) were the manufacturers understand how to improve their influenza vaccine supply support requirements and mitigate risk from supply as well.

In green, you can see some additional meetings that have been held through the year since the last VRBPAC meeting; particularly, the two HHS meetings there. The influenza vaccine virus mismatch and seasonal influenza vaccine improvements exercise that then fed into the WHO meeting in Hong Kong towards the end of November. And these were particularly with respect to thinking about the response to strategies to supply late or mismatched strains.

And this was particularly built across from the (H3N2) drift that occurred with the 2014-2015 season, but also we work within that environment to discuss things like the pandemic response, which is the meeting you can see here, on the corner between the June and July of 2015. And throughout these sessions, there's also been reference to assessing seasonal vaccine supply, an impact to the adherence to the Nagoya Protocol, which I'll briefly reference in a moment.

So how does it fit, in terms of seasonal influenza vaccine improvement? Well, from the meetings that we had with HHS, these were hosted June and November 2015, and had representation from HHS, FDA, CDC, NIBS, and the industrial parties, where we discussed a range of matters related to surveillance characterization of vaccine improvements and supply mitigation options. And these were pitched alongside a couple of scenarios.

Scenarios based on well, what if there was a delay in vaccine strain selection, through to April, what that might mean, in terms of delays of vaccine availability, and impact on immunization programs and schedules. What if then we had a delay through to July, in that situation, manufacturing would be well in process by then.

It might require potentially two different vaccines in the same campaign, and reduce uptake of late vaccine as a consequence. So that's quite an extreme situation, so in the rare circumstances of a late emerging strain, delaying selection to mid-late March. That might be considered acceptable if there are appropriate Canada vaccine viruses available, if the assay reagents are in process and the state of development.

And then the further rare circumstance of a significant delay, i.e., to beyond the April timescale, then this will need to be centrally coordinated. And if you think back to the 2009 (H1N1) pandemic, the kind of coordination, and the tightness of response then, was considered the requirement in that scenario for seasonal vaccine provision. So underlying this, they're given multiple challenges the preference is for no strain selection delay, at least from the manufacturers' identification to date.

A brief few words about Nagoya: Nagoya features, in the majority of the meetings, I referenced a little earlier, on that spreadsheet between the two VRBPAC meetings. It was developed from access and benefit sharing discussions at the convention of biodiversity 2010, and came into force in October 2014. And this describes access to genetic resources and

related traditional knowledge for potential research and utilization purposes.

And this is whereby users on providers in genetic resources and related traditional knowledge agree on a fair and equitable sharing of benefits arising from their utilization. You may be wondering why I'm mentioning this now. And that's because there is the potential impact to seasonal influenza strain availability as pathogens are included under the Nagoya protocol.

In other words, under the obligations of the Nagoya protocol, there will be the requirements negotiate terms of pathogen use, and that may currently include seasonal influenzas. So the bottom line there is that there is an unknown impact of influenza vaccine availability, for the U.S. market. However, the expectation is that there would be a delay of some manner or form, while those obligations, those negotiations were discussed and taken through.

So to conclude and allow us all to go for lunch; concluding comments. It's important then, that timely vaccine supply requires close collaboration and not just amongst the manufacturers, but amongst the global stakeholders. And communication is key as well, to ensure sufficient provision of

well-matched vaccine, and understanding of the strains, and understanding of the critical reagents, as we've just heard as well.

Timely strain selection ensures vaccine availability and use, and the preferences for current strain recommendation timelines. And if a change is required, do so for one strain by mid-to-late March. The impact of adherence to Nagoya protocol may be a delay in season influenza vaccine supply and distribution in the U.S.

So there are ongoing discussions with regards to that, as well, and the potential impacts, not just for the U.S., but globally. So with that, I'd like to say thank you very much for your attention, and I'll try to address any questions if possible.

DR. LYNFIELD: Are there any clarifying questions? Yes?

DR. WHARTON: Thank you. Given the mention of the Nagoya Protocol, I wonder if someone could provide just a little bit more information about, practically speaking, what we're anticipating might happen. I would expect there wouldn't be any impact on you, the inclusion of U.S. derived strains into anything, but just wonder, from those who are more familiar with

all this than I am, practically speaking, what we might be talking about here.

Dr. Katz?

DR. KATZ: Yes. It's a good thing. Thank you for raising this, Dr. Downham.

So many countries have signed onto the Nagoya Treaty, and this requires legislation in the country, in terms of how they will or will not share viruses. The first point to make is that the U.S. is not a signatory, so we cannot directly influence how Nagoya will play out. And I'm sure Dr. Gellin has been, also engaged in a lot of these discussions, but just to give you from the U.S. CDC perspective, and from a WHO Collaborating Center, what it could potentially mean to us.

Unless there is some global understanding of how countries can receive benefit sharing, which is a mandate of this protocol, we may be in a situation where CDC Collaborating Center is not able to receive viruses from countries that have signed on to Nagoya. This could also include other WHO Collaborating Centers, like Australia and London. So it could even restrict us sharing reference viruses between collaborating centers.

This is -- I mean we're very, very concerned about

this. It has -- nothing has happened yet, but it's only been just from the last, I believe from October, where it's really coming to law that the countries that have signed on, are now figuring out a way how to legislate this process. The other difficulty is that this was a treaty that was negotiated through international parties, mostly from ministries of the environment.

So in many situations, we think even that the ministries of health in different countries aren't really aware yet of the true impact that this could have. Recently, the most recent information that I have, is that certain countries -- so countries who have signed on, and an example is the Netherlands, they can make a statement that they freely, you know they give up their rights to benefits. They just want to share their viruses openly.

And this has been the basis. I mean this free sharing has been the basis of this global influence and network and vaccine virus selection for many years now. So countries can choose to do that, but we know certain countries, developing countries may not choose to do that, and really want to receive some sort of benefit.

And then it, there's a requirement between the

countries that are receiving the viruses, and potentially using them for vaccine virus purposes that then there's some agreement between the originating country. And I think that's what Dr. Downham is talking about.

The manufactures are concerned that if we choose a strain from a country that is requesting, sort of has signed onto Nagoya, and is requesting benefit sharing, then there is an agreement that has to occur, which could take many, many months.

And we know the timing of flu vaccines and that's not going to really allow us to freely use vaccine viruses for vaccine purposes from certain countries. That's the concern. So some countries, I believe it's the UK, the Netherlands, and I'm not sure; there's a third country, have approached WHO, and have approached the director general, to really make this a priority, and are trying to empower WHO to address this specifically for influenza.

But you can imagine that it also, since all pathogens technically fall under this Nagoya Protocol, it could affect many other pathogens of public health significance. Do you want to say anything?

DR. GELLIN: That was a great summary. Actually, what I was going to say is that Ruth introduced this section. We'll

have Matthew talk before lunch.

UNIDENTIFIED PERSON: Sorry.

DR. GELLIN: And this is a huge topic, and Jackie did a great job of summarizing it, and it's a conversation that many of us had with the flu vaccine manufacturers because they saw the potential here, given the tight timelines and the principal of sharing strains from many places, and those strains that then get shared on. So it further constrains a collaborating center from receiving those strains, and their ability to move things forward.

It is a big issue for which seasonal flu is, maybe the test case. But as Jackie said at the executive board, the UK brought this to the attention of Margaret Chan, and WHO is now going to take a look at this because if I understand it correctly, the only pathogen for which there is an agreement, an international agreement on this, is pandemic influenza.

Everything else, seasonal influenza, other viruses, other bacteria, and of particular interest to the UK was implications on antimicrobial resistance, and the sharing of those strains is what raised that issue to WHO, to take a look at this and try to figure out a path forward, so that this didn't become too cumbersome.

DR. LYNFIELD: Well, thank you for raising it, and for the discussion.

Dr. Monto?

DR. MONTO: How does the PIP Framework relate to this, the pandemic influenza?

DR. KATZ: Right. So the PIP Framework was --

UNIDENTIFIED PERSON: Not before dinner, now.

(Laughter.)

DR. KATZ: -- was specifically crafted to exclude seasonal influenza viruses, so it does not include seasonal influenza, so we can't at this point, use the PIP Framework as a demonstration of benefit sharing, for seasonal influenza viruses. At this point in time, but there is some discussion as to whether we just expand that, but it's going to take some time. It's complicated.

DR. GELLIN: But the same general is that if pathogens are to be shared, then there's some sharing of benefits, which is a whole range of things from co-authorship, to access to vaccines, and a number of different things, which is the larger construct.

DR. LYNFIELD: Thank you.

Dr. Moore?

DR. MOORE: Yeah, just a quick question. If we were to not accept the WHO recommendation for the (H3N2) antigen, and use last year's antigen, Switzerland, again this year, would that actually delay that manufacturer, or would it have no impact at all on the manufacturer -- on the timeline?

DR. DOWNHAM: It would potentially impact, as manufacturers would start to prepare the Switzerland stockpile, or reinstate the (H3N2) stockpile. So I believe, and I can't speak for all manufacturers, certain organizations have already started to stockpile the (H3N2) component, based on some of the surveillance, some of the meetings, some of the intelligence that's been gathered to date, in collaboration with the likes of the WHO, etc. So potentially, it would represent a delay in the event if the Switzerland was chosen.

DR. GELLIN: Matthew, if I can get you to comment on a few things? So I appreciated your animated graphic that ran off the page.

(Laughter.)

But I guess the question is, when it runs off the page, because all the other boxes stay the same size, and I'm curious about where industry is as far as, and maybe this is a question also for FDA, but what's happening now, as far as doing

the things that are in those boxes, in less time?

For example, production would be shortened if yield were better, and so, maybe if you could give us a global sense of how technology, and some of the investments that are made in pandemic preparedness might shorten those timelines so that it doesn't, ultimately run off the page.

DR. DOWNHAM: Yeah. So some of the discussions we've had, through the meeting schedule I showed earlier, have touched on the means of improving technology, improving analytical methods, applying new technologies, reverse genetics, etc., improving use of antibody reagents and so on. So there has been, or there is, an ongoing series of discussions to improve and maximize production and analytical capabilities.

And as I understand, from the meetings that we had with the HHS during November last year, there's a hit list of about 30 or 35 actions that are going to be worked through, addressing how to improve and then be more expeditious in manufacturing analysis.

DR. GELLIN: If I could make one other comment? That in this, and I'm glad that you introduced this, but in these table top exercises where we took a look at this to see how much of a delay of a newly emerging strain, how long you could wait

to finish the cascade, because clearly you could make the vaccine, but it would push things on.

And what was striking was the recognition that the international interlocking of this system, that these manufacturers are producing vaccine for many countries, and how at the far end of it, the vaccination, and many countries don't have much flexibility in altering the programs. I mean ours is, to some degree, as well, but some were much more rigid, as far as how a delay would make it much, much more difficult for them to mount a vaccination program, which highlights the global nature that's not just from the strains, but also on the relatively few manufacturers supplying so many countries.

DR. LYNFIELD: Okay. It is time for lunch. We are running a little bit behind and I suspect we will want to engage in discussion, so I'm going to ask people to come back at one o'clock sharp. I'm sorry that we are shortening lunch a bit, but I think we do need to do this.

We also have public comment scheduled, so we can't be too late for that. I also want to remind the Committee that we are not able to discuss the topics that we have been talking about today, because it is an open public meeting. So any conversation related to the work that we are doing today, needs

to be held until we return as a committee.

Dr. Vijh, do you have anything to add?

DR. VIJH: No. I think that's good. You're good. Yeah. Thank you.

Oh, that. Now that you ask, the Committee members should please go to the room in the back because the lunch is going to be brought there. So you don't have to go pick up your box lunches, but please head back to the room.

LUNCH

DR. LYNFIELD: Okay. I'm going to ask members of the Committee to please take their seats.

(Pause.)

OPEN PUBLIC HEARING ANNOUNCEMENT

DR. LYNFIELD: Okay. Now, we have gotten to the open public hearing portion of the agenda, and so I am going to read this statement:

"Open public hearing announcement for particular matters involving specific parties meeting, e.g., product specific.

Both the Food and Drug Administration (FDA) and the public, believe in a transparent process for information

gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with a sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsors' payment of your travel, lodging, or other expenses, in connection with your attendance at the meeting.

Likewise, the FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

OPEN PUBLIC HEARING

DR. LYNFIELD: And so at this point, we do have two individuals, who would like to make a statement. And we will listen to the statement, however, we will not respond to the

statement. So our first public speaker is Doris Boucher, from NYMC.

DR. Vijh: She said she doesn't want to (inaudible).

MS. BOUCHER: (inaudible)

DR. LYNFIELD: Oh. Okay. Then we have one public speaker. Thank you very much. This is Margaret Dayhoff-Brannigan; Dr. Margaret Dayhoff-Brannigan, from NCHR.

DR. DAYHOFF-BRANNIGAN: Hi. My name is Dr. Margaret Dayhoff-Brannigan. I'm the Patient Network Project Manager at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policy makers. We do not accept funding from pharmaceutical companies and therefore, I have no conflicts of interest.

Thank you very much for the opportunity to speak here today. I completed my PhD in biochemistry and molecular biology at the Johns Hopkins School of Public Health. I bring a perspective as both a researcher and an advocate for public health safety here today. I'm here today to express our very strong concerns about the contradictory statements in evidence regarding flu vaccines and antiviral medications from two federal public health agencies: The FDA and the CDC.

Patients and physicians are not well served when the CDC seems to be promoting medical products, rather than providing facts made available by FDA analysis. An effective flu vaccine is critical for public health. The 2014-2015 vaccine had only a 23 percent efficacy, while this year's vaccine efficacy was an improvement, it's important that we implement strategies to improve the consistent efficacy of the influenza vaccine.

When the vaccine does not work well, people think they should not bother to get it. This is bad for both pharmaceutical companies, who have unused doses of vaccine, and for the general public that's less protected. We applaud the FDA and CDC for changing the recommendations for children, to reflect the poor efficacy of the live attenuated influenza vaccine or nasal spray.

We hope the FDA will continue to look carefully at whether the Agency should rescind approval for the flu nasal spray, if it continues to show significantly lower efficacy than the standard flu shots toward certain flu strains. There's another problem, however, that I want to talk about today.

The CDC has strongly encouraged patients to use antiviral medications if they get the flu. However, evidence

shows how little benefit Tamiflu offers, as well as significant risks for children. Tamiflu must be taken within 48 hours of symptoms to be effective, and even then, it will only help you get better one day sooner.

That would be acceptable if Tamiflu was inexpensive and had no risks, however Tamiflu is very expensive for many people, and does have risks. Patients deserve unbiased information about the risks and benefits, but CDC is providing biased information. It exaggerates the benefits and minimizes the risk.

The CDC's oddly promotional behavior regarding Tamiflu seemed strange to us, until we read in the *BMJ* that the CDC Foundation is accepting directed contributions from Roche, the makers of Tamiflu. These contributions are then provided to the CDC, creating a clear conflict of interest. Millions of Americans count on the CDC to make health recommendations and they depend on them to conduct research impartially.

The CDC has been strongly recommending Tamiflu, despite controversy over its effectiveness. The FDA and CDC present conflicting information about the efficacy of Tamiflu in high risk populations. Tamiflu labels provide FDA-approved information that is starkly different from what is recommended

by the CDC.

The FDA states that "Tamiflu has not been tested in patients with chronic cardiac disease, or respiratory disease." However, the CDC provides an informational handout that states, in bold, that "if you have a chronic illness, such as asthma or chronic heart disease, antiviral drugs can mean the difference between a mild illness and a hospital stay." There is no evidence to back up that statement.

Thank you very much for your time.

DR. LYNFIELD: Thank you. Okay. I don't think we have any additional public speakers, so at this point, we are now moving to discussion. And what I would like to do is open the floor for discussion. I know that we've had some initial clarifying questions and conversation this morning, but why don't I first open up and see if anyone has any issues to bring up.

COMMITTEE DISCUSSION

DR. LYNFIELD: Dr. Sawyer?

DR. COOPER: Oh, I'm sorry.

DR. LYNFIELD: I'm sorry.

DR. COOPER: Perfect timing.

DR. SAWYER: You can go first.

DR. LYNFIELD: Okay. Dr. Sawyer is yielding to Dr. Cooper.

DR. COOPER: We'll be here all day. I just want to clear up your question regarding where the B/Yamagata viruses in our analysis came from. It turns out they came from throughout our network: Egypt, Germany, Washington State, California. And the B/Victoria also comes from a variety of places: Japan, Egypt, and Washington State, as well.

I'd like to thank my colleagues USAFSAM, who furnished me with this information. They attend this meeting every year. So thanks.

DR. LYNFIELD: Thank you very much, Captain Cooper. That actually does remind me. We had a couple of questions for Dr. Grohskopf from this morning. Lisa, did you get a chance to --

DR. GROHSKOPF: Yes.

DR. LYNFIELD: -- take a look?

DR. GROHSKOPF: Yes. I got some additional information. With regard to the second question, which had to do with whether or not we had anything else we could say about the (H3N2) isolates, in cases, in the U.S. Flu VE Network data.

The investigators feel that they're really isn't enough to draw any conclusions, however the VE for all A, all influenza A, is very similar to the VE when the (H1N1) isolates are pulled out, if that's helpful. But I can't get any specific information about those cases, aside from that.

With regard to the earlier question, which had to do with, in the, I think it's the third slide, which was the slide that depicted the virologic surveillance results from the Public Health Laboratories, that is submitted to the CDC on a weekly basis.

The question was, I believe, "What proportion of the influenza B isolates, were not subtyped?"

And in what I have here is actually that same information for week eight, because the slides were only just updated within the last hour or so, but the numbers are not very different, I would gather, from the week seven data. Among the influenza B isolates, just for week eight, the most recent week we have data, 56.4 percent were not sub-lineaged. Lineage testing was not performed. And among all of those cumulatively, since October 4, 2015, lineage testing was not performed for 45.7 percent.

DR. LYNFIELD: Okay. Thank you very much. I really

appreciate your checking that.

DR. GROHSKOPF: You're welcome.

DR. LYNFIELD: Dr. Sawyer?

DR. SAWYER: Yeah. My question relates to this influenza B sub-lineage topic. And as not a long-term flu watcher, I'm interested in the perspective of those who have seen the B strains come and go. Dr. Katz made the point that they tend to cycle every few years. I'm wondering how regular that is and how often, if you can tell me, it started to look like it was coming, and then didn't come because again, like many of the comments earlier this morning, it seems to be pretty close to make this call between Yamagata and Victoria.

DR. KATZ: Yeah. I don't have the historical knowledge that my predecessor had, I'm afraid, but I do know that the lineages do cycle. I can't say that there's predictability, that there's a predictable pattern every two years or three years. I can't say that.

All I can say, I think, is what I said this morning, is that we know this shift from one lineage to the other happens with some regularity. It may not be every -- or it continues to happen. Maybe that's a better term to turn a phrase.

And just from the available data that we have seen

globally since, I would say, August, sort of the end of the southern hemisphere season, there certainly seems to be that shift that is happening at this time. Whether that will happen, and it will -- B/Victoria will predominate in the U.S. next season, I can't tell you that.

DR. LYNFIELD: Dr. Moore?

DR. MOORE: Yeah. I'm a little bit concerned -- not concerned. At least I'd like someone who knows more about flu, which is most of the people here at this table, than I do, to explain to me why, or at least convince me, as to the (H3N2) antigen change that we're making. What is really to be gained by that?

And especially in light of the fact that the year before this year, we had a pretty bad epidemic of flu, from (H3N2), guessing wrong on that antigen strain. And then we, this year, either we have exhaustion susceptibles, or effective vaccine coverage. And it seems to be working. So I want to know why we want to change.

DR. KATZ: Okay. Just to address the last question. I think H3 is, globally on the downturn this year. It was a lot of (H3N2) in the previous couple of seasons and that maybe because so it may mean that the immunity, it has built up

naturally, as well as, through vaccination.

I mean there are many parts of the world that don't vaccinate a large portion of their population. And I would say, overall, we've seen a very modest (H3N2) season this year globally. To speak to the WHO recommendation to move to the Hong Kong/4801, and this is sort of data that we've gathered, I mean this decision was first made in September last year, for the southern hemisphere, and there was always some concern that because the 3C2A genetic group was predominant, we believe that that is the virus that we need to follow most closely, and track.

It does look like the 3C3A viruses -- although there's been some modest activity in Europe -- they are not the predominant. They haven't been the predominant strain, at all, since these viruses emerged, or since these viruses took off. And the earlier decision to go with Switzerland was, there was more 3C3A at that time, but it was largely based on the availability of the Switzerland vaccine component, a candidate vaccine virus.

This time last year, we knew the 3C2A viruses were beginning to predominate, but there was very limited data, and not enough information on candidate vaccine viruses. So these

are the egg-grown viruses. We didn't understand the properties of the 3C2A viruses well enough, and so the decision in February of last year, for the WHO, was just go with Switzerland.

Between February and September of last year, there were many candidate vaccine viruses that for the 3C2A, what we call the "Hong Kong/4801-like" viruses, there was a lot of work ongoing in multiple re-assorting labs, including Dr. Boucher's lab in New York, to make candidate vaccine viruses available for the 3C2A subgroup.

And so, in September, we had a body of data that was more convincing to us, that the Hong Kong/4801-like viruses were not only genetically a better match for the predominant circulating strain, but that if you looked at the egg-grown viruses, the antisera in our antigenic tests appeared to do a better job of covering the circulating viruses than did the antisera to the egg-propagated Switzerland.

And so, it was the decision in September -- and again, now, in February at WHO was really an incremental improvement in the (H3N2) vaccine, to really better match what we know is the predominating (H3N2) virus and to be closer to genetically to the virus as it's going to continue to evolve. And we think that it's going to evolve in this direction of the 3C2A viruses.

DR. MOORE: And just to follow up, and this refers back to your 22, which is a cladogram for the HA genes, for the (H3N2)'s. The 3C2A group looks, the Hong Kong group, it looks like a fairly distant genetic splinter off of a main group of the 3C2A. So just based on phylogenetic divergence alone, wouldn't it make more sense to pick a strain that is in the center of that clade?

UNIDENTIFIED PERSON: (inaudible)

DR. MOORE: Yeah. Your phylogenetic tree of --

DR. KATZ: Correct.

DR. MOORE: -- the hemagglutinin gene.

UNIDENTIFIED PERSON: (inaudible)

DR. MOORE: It is --

DR. KATZ: Twenty-two.

DR. MOORE: -- slide 22 that I have in the corner.

DR. KATZ: Right. So the Hong Kong is sort of a bet at the base of that, right.

DR. MOORE: Right.

DR. KRAFT: But so for any virus to be a reference virus, and to be a potential vaccine virus, it has to be sort of a little bit behind. It has to be older than the emerging, what you're seeing here, is that emerging group in the oranges and

greens and blues, of the most recent viruses, but Hong Kong still represents that group very well, even though it's sort of at the base, and a little bit back.

And it may actually mean that it is a better -- I'm trying to see where the consensus -- it's right, actually --

DR. KATZ: Can I just point it out?

(Pause.)

DR. KATZ: Thank you. So there's Hong Kong, and right above it, this says, "2016 (inaudible) 3C2A Consensus." So actually, Hong Kong is quite close to the consensus of all of these emerging 3C2A viruses.

DR. LYNFIELD: Dr. Andrews?

DR. ANDREWS: I don't know if this matters, but are these different subtypes, the type of flu that you get from it, is it just as bad as any other? Because I am thinking that you know viruses could, in a perfect world, drive what -- you know what the -- I mean eventually drive them away, hopefully, but what kinds of variants there are, and whether if we ease off of one, do we let that you know come up in prevalence, if we guess wrong.

And with more and people being in health plans, where they get dinged -- I get dinged $100 a month if I don't, in the

State employee plan in Connecticut, if I don't do a whole list of things, including get a flu shot. I would imagine that more and more people are going to be getting this shot, and that it might be, not just something you're reacting to what's going on, but you might be able to drive it.

And are there variants that really make people very, very sick that are more likely to kill, and we want to make sure that's included. That gets a higher priority on the list, even though it may not be as prevalent. Was it a stupid question?

DR. KATZ: No, it's not a stupid question. So I would say, I mean it's clear that we have an (H3N2) season, a predominant (H3N2) season. There's a higher morbidity, particularly in the older adult population, and we tend to have what we call more severe seasons.

Is one subgroup, you know more responsible or cause more severe disease? We don't think so. We have that question -- moving to (H1N1). We have that question quite frequently, and we've had it again this season, because I think, as I mentioned in my talk, we have had reports, not only in the U.S.

There was a report yesterday just from Mexico, from Europe, the Middle East. Whenever we have an (H1N1) pandemic 09 virus season now, it appears to also be associated with more

severe disease in a portion of the population. Again, we don't think there's anything, that there is some unique variance within that are responsible for that severity.

We're looking we continue to look at this. We've looked at this for years always taking viruses from severe cases, fatal cases, and looking at their full genome and saying, asking, is there anything different in these viruses, compared with the other viruses of this, from individuals of the same age group, in the same regions, and we really can't see anything unique.

I think severity is very complicated, and there are many host-related factors as well. I understand your point. I think we want a vaccine that can be protective against you know, both H1's and ideally, both B's regardless of the level of severity that we might see with one, over the other.

DR. LYNFIELD: Thank you.

Dr. Bennink?

DR. BENNINK: Yeah. I touched on this wrong before, but I want to go back to this, the term "like" in terms of this, and the H3 viruses, and the list of viruses that you know that are here that are possible, in terms of the H3 that are considered "like" in that sense. And if you look at the ones,

at least that the industry sort of listed here, evaluated for this thing. And I don't know if that's the right -- or we could look at the FDA ones.

You know, in the data that you presented, the data is not always there for in those tables, at least I didn't -- maybe I just missed it or something, but have you done a really good antigenic comparison of the like viruses that you do, and do you -- the real comfort in terms of saying, you know, any one of these viruses is just as good, whether it's cell-based, whether it's egg, whatever, you're really comfortable that the cross reactions in terms of antigenicity is very good?

DR. KATZ: Okay. So I wouldn't look at the list from industry. Some of these are emerging variants and not -- I mean they would be considered Hong Kong/4801-like, but not all of these are representatives of what we would be using as a reference prototype virus, and be considering for vaccine production, at least at this time.

So the primary candidate vaccine viruses are Hong Kong/4801 itself; Hong Kong/7127, I believe; New Caledonia/71 and I guess I should (inaudible).

UNIDENTIFIED PERSON: Yeah.

UNIDENTIFIED PERSON: Yeah.

DR. KRAFT: The FDA one, yeah. And so, and Victoria/673, although I'm not -- maybe FDA can speak to this -- I'm not aware that we have reassortants for that. So these viruses, obviously by their origin, have emerged in different areas. The New Caledonia one was a virus that was developed or isolated by the Australian lab, and was actually one of the earlier proposed vaccine viruses.

At that time, we just didn't have enough information about it. We knew it wasn't Switzerland-like, and so, we just didn't have enough information to recommend it as a virus. So it was really only when we identified the group of viruses that what we refer to as "Hong Kong/4801-like."

So once we identified Hong Kong/4801 as our sort of prototype virus, what happens is then the different centers go back and look at some of these other candidates, for which they also had an egg-grown virus, and they do antigenic testing, and confirm that the reactivity is sufficiently similar to Hong Kong/4801, that we call it Hong Kong/4801-like.

DR. BENNINK: Yeah. I think it would, for me anyway, when we look at them, I think it would be useful, at least as the Committee looks at it, to see, you know, in a sense like you have these table that you have here, an assay where you actually

-- an antigenic assay, where you actually compared those in that sort of sense. Then you know that you're really comparing all of them in that way.

DR. LYNFIELD: Go ahead.

DR. BENNINK: I'm going to go on a different tangent, and ask Jerry in just a second, because in the previous years, or so, there was some, and it was brought up by the other -- and I'll just make a mention here, if you want to say anything you know in terms of the live attenuated.

In the data that the Department of Defense presented here, there was at least one that was statistically saying -- that looked like it was, maybe even better than the inactivated in this particular case. But can you give us an update or something, in terms of what kind of interactions, in terms of -- that you might have had that you might want to speak about, or not?

DR. WEIR: (Inaudible - Off Mic)

DR. BENNINK: You would rather not say anything?

DR. WEIR: (Inaudible - Off Mic)

DR. BENNINK: That's okay.

DR. WEIR: (Inaudible - Off Mic)

DR. BENNINK: I'm just curious, because we have in the

past, you know had some --

DR. WEIR: (Inaudible - Off Mic)

MS. GRUBER: I don't think that we can speak here and talk about the specifics, but I guess we can say that we have had discussions with the manufacturer. Yeah.

DR. LYNFIELD: Dr. Sawyer?

DR. SAWYER: Well, speaking of the different vaccine products available, we could avoid this whole Victoria versus Yamagata debate, if we were using more quadrivalent vaccine. I'm wondering if anybody here knows, for this current season, what the proportion of distributed doses are that are quadrivalent versus trivalent, and if anyone from manufacturing is willing to tell us what the plans might be for the coming year.

DR. LYNFIELD: Dr. Katz?

DR. KATZ: Yes. I don't have the exact numbers, but I believe it's a little over 50 percent of the influenza vaccine available in the U.S. market is quadrivalent.

DR. LYNFIELD: Any comment from the manufacturers?

DR. DOWNHAM: It's a long way to walk, to say no, I'm afraid there isn't. I don't have data on the distribution of quadrivalent and trivalents, unfortunately. Sorry about that.

DR. LYNFIELD: Other comments or questions?

MS. COST: (inaudible) Captain Cooper, I'm allowed to comment for DOD. I can just speak to the fact of what we saw on the active duty population, that about 30 percent of the active duty population received the quadrivalent vaccine. The rest was receiving the trivalent vaccine.

DR. LYNFIELD: And I'm sorry. Can you state your --

MS. COST: I'm sorry. Angela --

DR. LYNFIELD: -- name and your --

MS. COST: Angela Cost, with the Armed Forces Health Surveillance Branch.

DR. LYNFIELD: Thank you very much. Are there any other points for discussion? Dr. Wharton?

DR. WHARTON: Well, I have to say, from having attended this Committee for a number of years, it is gratifying that we now do have quadrivalent vaccines that contain both B lineages, because historically, this was such a difficult decision for the Committee.

The information is -- you know, it's very challenging to make that decision. And it really was out of dissatisfaction with our ability to make a prediction that was very accurate that really led to the Committee's interest in the development

of vaccines that include both B strains.

And of course it is wonderful that we now have them from multiple manufacturers and that they account for a significant part of the market. But there still seems to be some issues that I have to say, I don't fully understand, around the (H3N2) component. And I wonder if, at some meeting in the future, it might be possible to spend a little time delving into that complex set of issues a little bit more deeply, to see if there's -- to get a better understanding of it, and identify any issues that might be amenable to better solutions.

DR. LYNFIELD: And can you articulate a little further what you have in mind? Is it the challenge of vaccine ineffectiveness amongst (H3N2)? Are there other issues?

DR. WHARTON: Well, I am probably not the person best suited to answer that, but there appear to be a variety of complex issues related, both to the biology of the virus itself, our ability to -- the laboratory methods we have to evaluate it, and the complexity of those, as well as vaccine effectiveness, and it's probably some other things, too.

DR. LYNFIELD: And I'm going to take the Chair's prerogative, and ask Dr. Monto, did you have a comment regarding the (H3N2) situation?

DR. MONTO: Yes. I think I agree totally. We've got a problem here, which has been going on for a number of years. Last year, it was even worse because we had drift, in addition to the issues of the H3 not behaving as well as we would like, in terms of vaccine effectiveness. This is the component of the vaccine we most need to work because it's the (H3N2) that causes typically most of the excess mortality we see in the risk populations.

There's also an issue, which has emerged again and again in different studies of prior year vaccination. Here, we're recommending that vaccine be used on an annual basis. And is there a way through strain selection that we can avoid this kind of an issue?

It seems to be more an (H3N2) issue. I think it may require an interagency kind of response, rather than simply an FDA response. But the FDA can take the lead, given the role of strain selection and other activities that FDA carries out, in organizing some kind of -- maybe an appropriate meeting targeted on this question would be the first step, and then it could be figured out, how to address it, in terms of the different components of the government.

DR. LYNFIELD: Dr. Kotloff?

DR. KOTLOFF: Something that I'm having a hard time getting kind of my brain around, is the substantial variability in vaccine effectiveness estimates, and it would seem that you know I think it's very nice when you have a, kind of convenient sample of cases and test negative controls, and can measure effectiveness.

But I think for many reasons, including you know what we tell the public about the value of this vaccine, and understanding the value of the different formulations of vaccines against different influenza types that if we could really systematically have a well-designed powered vaccine effectiveness trial, on an annual basis.

I don't think the sample sizes are huge for this type of study, but that covered both effectiveness of the live and the inactivated vaccine, that looked seriously at different age groups and was powered to look at that. And then of course that's able to look at different strains of flu, which is harder for us to control. But it just seems that's such an important piece of information that's missing.

DR. LYNFIELD: So I don't know if Melinda or Jackie want to comment. I know CDC does have a VE Network.

DR. KATZ: Yeah. I think we're trying to do that.

And you heard some of the interim estimates presented today. It's just at this time of year we're never going to have the final result.

But the CDC has, since I think 2004-2005, has initiated the U.S. Vaccine Effectiveness Network and its multiple sites, it's very large numbers of individuals enrolled, and I think it's -- I mean there's always ways to do things better, but we are a little bit at the whim of what's circulating that year, and when it's circulates, to really be able to provide the estimates. But I think they're --

UNIDENTIFIED PERSON: That there will be more end of season.

DR. KATZ: There will be, yeah. We'll have the final data sort of coming out, and yeah, Arnold is the expert on this.

DR. MONTO: Well, we're one of the sites.

DR. KATZ: Right, of course.

DR. MONTO: And so I can speak to the kind of approach that is used, which is not a convenient sample. There are clear eligibility characteristics for being considered as somebody whose test is either positive or negative; in other words, whether they test positive for flu, or negative for flu. The network has five sites; it's being re-competed right now.

There's also now, a vaccine effectiveness hospital network. This is the first year of the hospital network, because one of the deficiencies was that we were looking at ambulatory cases and the hospital, the more severe illnesses were being missed, and very often, the illnesses in older individuals, because ambulatory networks typically don't take care of a whole lot of older people. They take care of a lot of younger people.

The problem in these networks is that we are totally dependent on the vaccines that are used. It's observational, therefore, given the issues related to the live attenuated vaccine, we are probably going to see less live attenuated vaccine use in the current year. The data from the network was very useful in past years to evaluate the live attenuated vaccine.

Similarly, we are going to find it difficult to draw conclusions about the multiplicity of different kinds of influenza vaccines that are coming out, in terms of varied effectiveness, if such differences exist. So, but there are ways around this in terms of targeting, if you could target certain areas where these networks are existing, in terms of what vaccines are used.

But it's been a -- I think it's because of these networks that we are now recognizing that there is a problem with the (H3N2) vaccine. And one thing that is very clear, given the similarity over the years in methodology, we can now create a hierarchy of which vaccines are working reasonably well, and which are not, and the one that isn't is (H3N2).

DR. LYNFIELD: I think what I would like to do is just have the opportunity to go person by person around the table, and just make sure there aren't any other questions or issues to bring up.

So Karen, let's start with you.

DR. KOTLOFF: I've asked my question, thanks.

DR. SAWYER: I'm good.

DR. MOORE: Just a brief comment or maybe it's a question. And it seems to me, as a non-expert in flu that we're missing a very key component, in predicting vaccine efficacy based on HI testing alone, which is, the vast majority of the immunologic data that we're given by CDC and WHO.

And so, one thing that I think might be helpful, is, if we now at this point in time, step back and say, what other immunologic tests, whether it's neuts, whether it's NA testing, or even NA expression, obviously some strains are very low

expressers that are a little bit more predictive, in what vaccines are likely to have broad cross-reactivity, rather than focusing only on HI data alone, or at least primarily on HI data, and then HI genetics. That worries me at least a little bit, as a non-expert in evaluating this.

DR. KATZ: So are you worried about the focus on the hemagglutinin, or just the fact that we use the focus on the HI assay, itself because we are, for (H3N2)'s for sure, using neutralization tests more and more. The issue is, if we have to characterize thousands of viruses, antigenically with the reference ferret antisera, the HI is the quickest, fastest, and most efficient way to do that.

We're working on developing higher throughput approaches for the neutralization assay. We're just not quite there yet.

DR. MOORE: Bravo.

(Laughter.)

DR. MOORE: Please do that. At least I would think, I would feel much more confident on those data than any variant of HI alone. And I know that it's very hard because you do have to do things rapidly, and it's a relatively easy test, but for some reason, we're just not capturing all the data we need, in order

to make a really good prediction as to what is a broadly efficacious vaccine, it seems to me.

DR. LYNFIELD: Yes, Dr. Ye?

DR. YE: Well, I just want to comment on the assays. I think, now, for the human serology studies, we also include microneutralization in human serology studies, and that I think is similar to the study using ferret. Other than, in the human we confirm that the assay, you know HA assay.

So you know whatever the result come from the HI similar to the assay from microneutralization. And those are, I think for HI assay, you are looking for the virus entry that bind to the host receptor. In the first step of an infection, where, the microneutralization you're looking for the whole cycles of the replication that not only look for HA assay, or HA function, but also looking for some NA function, because unlike HI assay, you can add any inhibitors, just measure HA assay.

Where, in microneutralization you cannot add anti-HA there because you abolish virus replication you cannot do it anyway. I think both assay they are an advantage and a disadvantage. You've got to add together to give you whole picture.

DR. LYNFIELD: Thank you. Dr. Long?

DR. LONG: Infectious disease doctors like single pathogens, a good vaccine that works once, lasts a lifetime, and the disease is gone. So I always come to this meeting, influenza, paying really careful attention. And by ten o'clock I have a very big headache because the pathogen never stays the same.

It's very, very clever. There are many, many, many pathogens under the rubric of influenza. It's a mucosal disease. A natural disease doesn’t provide long-term protection.

We are trying to go about at this by multiple ways; none of them is perfect even for the short time after the vaccine is administered. So I'm comfortable trying to follow the footprints of the virus that we have seen today, I think, pretty elegantly, put out in front of us.

And I'm very pleased with what happened in the last year of the predictions, in the match. And so I'm trying to concentrate a little bit more. I'm not trying to solve a big influenza problem today, but trying to with the things that we have in front of us, what's the best direction to go. So I'm good.

DR. LYNFIELD: Great. Dr. Monto?

DR. MONTO: Well, I think I've said enough, but I'll add one point, and that is, last year our outbreak in Michigan and in much of the country, was an a H3 [sic] AA32C virus. And Switzerland, which is currently in the vaccine, would not have matched it. So that's for me the reason to move on, to the Hong Kong.

DR. MCINNES: I have no questions, no comments.

DR. LYNFIELD: Thank you. Okay. Dr. Gruber, yep, but maybe she would like to make a comment.

DR. GRUBER: I do not want to make a comment.

(Laughter.)

DR. LYNFIELD: Okay. Thank you.

DR. GOLDBERG: Hi. This is Dr. Goldberg.

DR. LYNFIELD: Great.

DR. GOLDBERG: Am I correct, in assuming that if we go with these recommendations, there will not really be any kind of production delay?

(No response.)

DR. GOLDBERG: Of any significance? Or am I, did I miss something?

DR. LYNFIELD: One of the manufacturers will come to the microphone.

DR. GOLDBERG: Okay.

DR. LYNFIELD: And can you be a little more specific, Dr. Goldberg, in what you're asking when you say, "These recommendations"?

DR. GOLDBERG: Well, I guess, I mean it's hard because I don't have any hard copy of the presentation, but as I was looking at it, it did not appear from the slides, that with these recommendations for any changes, that there would be anything that resembled a really significant delay in production, because there was too much to do to get it to work.

DR. LYNFIELD: Okay. So to clarify, when you say "these recommendations," are you --

DR. GOLDBERG: The manufacturer --

DR. LYNFIELD: -- referring to --

DR. GOLDBERG: -- if we (inaudible) --

(Crosstalk)

DR. LYNFIELD: -- to the ones --

DR. GOLDBERG: -- the changes.

DR. LYNFIELD: -- that the WHO recommended, or --

DR. GOLDBERG: Right.

DR. LYNFIELD: -- what are -- okay.

DR. GOLDBERG: Right. Sorry.

DR. LYNFIELD: No, no.

DR. GOLDBERG: Okay.

DR. LYNFIELD: I just want to clarify that. So you're asking if we followed the WHO's recommendations from last week, would one expect an on-time process.

DR. GOLDBERG: Relatively on time, yeah.

DR. DOWNHAM: I suggest the answer to that is we would be able to meet the timelines per usual. Going back to the meetings that we've had through the WHO, through the course of 2015, many within the manufacturing sector have the head's up there was a likely change, particularly with the (H3N2)'s. So obviously I can't speak for all manufacturers, as usual, but I would suspect that we are all bases loaded and ready to go.

DR. GOLDBERG: Thank you.

DR. LYNFIELD: Thank you.

DR. GELLIN: So just on a finer point, Matthew. So, but weren't the strains that are on the table now, are those that have been in the vaccine, in the southern hemisphere for the past six plus months. Right?

MR. DOWNHAM: Correct.

DR. GELLIN: Okay. Thank you.

DR. BENNINK: I think -- I'm fine, thank you.

DR. LYNFIELD: Okay.

MS. ANDREWS: I don't have any more questions, but just a comment. I'm new to this Committee, and a consumer representative (inaudible) on health systems. I'm really impressed by how much working butt goes into the flu vaccine, and you know the fact that you get it wrong, now I get why.

(Laughter.)

MS. ANDREWS: My head hurt by ten o'clock, too. I'm impressed.

(Laughter.)

COL STANEK: This is Colonel Stanek. I don't have any issues, but I do want to say that obviously it's a difficult decision, and every year that I come to this meeting, I always appreciate the in-depth discussion and the presentations that we get, really are unparalleled. So thanks, to everyone who helps give those presentations.

DR. KATZ: I just want to apologize for making everybody's heads hurt.

DR. WHARTON: I don't have any questions. I would like to say that it's amazing the amount of information that's available, and I think that is part of the reason why it gives people a headache. There's a huge amount of information that is

collated globally.

There are choices to be made. There are decisions because there are options, because we have so much information, and that's really a better place to be than having less.

DR. AIR: Yes. I also would like to congratulate everyone on the amount of information, and also the realization for Dr. Katz and Dr. Ye that you have to look at the whole virus life cycle to predict the effect, and not just binding. And I think this is a big step forward.

DR. GELLIN: I don't have anything else to add, except that as we all learn, while we do this once a year, and the flu season is seasonal, this flu thing is 24/7 365. And Jackie and her team and the vast global team that's responsible for making sure all this happens is doing this every day.

DR. LYNFIELD: Dr. Vijh, any comments?

DR. VIJH: No.

DR. LYNFIELD: No? Yeah. I also really want to express my great appreciation for all the work that people do to be able to bring us these data, and to explain the data to us. So we're very grateful to Jackie, and to the Department of Defense, and to the FDA, and to those associated with the WHO system. So thank you.

Okay. Well, I'm going to turn it over to Dr. Vijh for a few moments, who will lead us through the next part of the meeting.

VOTING

DR. VIJH: So basically, we have four questions to vote on, and the Committee has to vote on. They're in front of you on the monitors and the screens. So it's going to be 1(a), (b), and (c), and then 2 for the quadrivalent.

So the way it works, if you've not used the system before. In front of your -- on the microphone, you have, it says "yes," "abstain," and "no." So we use and electronic voting system, in which the votes are cast simultaneously.

And while you're in the process of voting, the buttons will keep flashing. And Derek there is going to start the machine and it'll start flashing. Whatever you vote, please press yes, no, or abstain, depending on your vote for each question; so 1(a), 1(b), 1(c), and then 2(a), so you'll have four voting things to go through.

And while the vote is open, if you'd like to change your vote, simply press a different button, and this will change your vote for the record. While you're voting it's private. And after the buttons are finished flashing and the voting is

officially closed, your vote is locked in, and the vote will then be displayed on the T.V. screen, and I will officially read and tally the votes for the record. Do you have any questions? Anybody?

DR. GOLDBERG: Hi, it's Judy Goldberg. How do I vote?

DR. VIJH: Yeah, Dr. Goldberg, why don't you, when we go through the process, you can email me your vote, and I can -- the machine has been programmed for me to press your vote, and to be displayed on the screen.

DR. GOLDBERG: Okay.

DR. VIJH: Thank you for asking that.

Just give me one second.

(Pause.)

DR. VIJH: Derek, are we good?

(No audible response.)

DR. VIJH: So for the first question for the Committee:

Question 1(a): "For the composition of the trivalent 2016-2017 influenza virus vaccine in the U.S., does the Committee recommend: (a) inclusion of A/California/7/2009(H1N1)pdm09-like virus?"

The buttons are flashing on your microphone. Please

press yes, abstain, or no. I'm still waiting for Dr. Goldberg's email.

(Pause.)

DR. GOLDBERG: I'm sending one, and wasn't fast enough to get them all done.

DR. VIJH: So what are you saying? Did you say yes?

DR. GOLDBERG: Yes. I sent you the first, it would be question one is answered.

DR. VIJH: Okay.

DR. GOLDBERG: Do you have it?

DR. VIJH: Just a second.

UNIDENTIFIED PERSON: Five?

DR. VIJH: Yes.

DR. GOLDBERG: Okay.

UNIDENTIFIED PERSON: Two, one (inaudible).

DR. VIJH: So it's the other way around for me. That's okay. Let me just -- give me some, a few seconds to just look at this.

Okay. So I'm going to read the vote officially for the record. It's Dr. Bennink, yes; Dr. Andrews, yes; Dr. Stanek, yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin, yes; Dr. Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr.

Sawyer, yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and Dr. McInnes also votes yes; so that's a total of 14 unanimous votes of yes for the first question. Thank you.

So we can now move on to the second set of strain.

Question: "For the composition of the trivalent 2016-2017 --

DR. MCINNES: Dr. Vijh? Dr. Vijh, hold on.

DR. VIJH: Yes?

DR. WEIR: We just noticed -- several people did -- the Hong Kong/4804 is actually 4801. So it's a little typo that we'll need to correct for the record.

DR. VIJH: So could you please change the 4804 to 4801?

DR. LYNFIELD: Thank you.

DR. VIJH: Derek, are you going to change it?

DR. LYNFIELD: Yeah.

DR. VIJH: Thank you so much. That's a good catch before we voted.

(Laughter.)

DR. VIJH: Question 1(b): "For the composition of the trivalent 2016-2017 influenza virus vaccine in the U.S., does the Committee recommend (b) inclusion of A/Hong Kong/4801/2014

(H3N2)-like virus?"

So the buttons are flashing in front of you. Please choose one of the options: yes, abstain, or no.

So it's Dr. Bennink, yes; Dr. Andrews, yes; Dr. Stanek, yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin, yes; Dr. Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr. Sawyer, yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and finally, Dr. McInnes, yes; so it's a total of 14 votes of yes, unanimous vote. Thank you.

Moving on to the next voting question.

Question 1(c): "For the composition of the trivalent 2016-2017 influenza virus vaccine in the U.S., does the Committee recommend the inclusion of B/Brisbane/60/2008-like virus B/Victoria lineage?

So Dr. Bennink, yes; Dr. Andrews, yes; Dr. Stanek, yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin, yes; Dr. Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr. Sawyer, yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and Dr. McInnes, yes; so again, it's a unanimous vote of 14 yes, for the record. Thank you.

Dr. Goldberg, you could send me the vote for the second question. I'm going to read it shortly.

So moving on to the quadrivalent vaccine:

Question: "For quadrivalent 2016-2017 influenza vaccines in the U.S., does the Committee recommend the inclusion of a B/Phuket/3703 [sic] 2013-like virus B/Yamagata lineage as a second influenza B strain in the vaccine?"

The buttons are flashing on the machine. Could you please vote: yes, abstain, or no.

DR. KATZ: I think the B/Phuket should be 3073.

DR. VIJH: We have to redo this. What is it?

UNIDENTIFIED PERSON: 3073.

DR. VIJH: Officially?

UNIDENTIFIED PERSON: It said 3703.

DR. VIJH: Yeah. It's 3073.

DR. LYNFIELD: Thank you, Dr. Katz, for noticing.

DR. VIJH: So I'm going to read this. Do I need to read it again, though?

DR. LYNFIELD: (No audible response.)

DR. VIJH: Yeah. Let me read this again for the record.

Question 2: "For quadrivalent 2016-2017 influenza vaccines in the U.S., does the Committee recommend the inclusion

of a B/Phuket/3073/2013-like virus B/Yamagata lineage as a second influenza B strain in the vaccine?"

Please vote: yes, abstain, or no.

So the vote is: Dr. Bennink, yes; Dr. Andrews, yes; Dr. Stanek, yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin, yes; Dr. Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr. Sawyer, yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and Dr. McInnes, yes; a vote of 14 unanimous yes.

So that concludes the voting for today's meeting. I hand over the meeting to Dr. Lynfield.

ADJOURNMENT

DR. LYNFIELD: Well, I want to thank all the members of the Committee, as well as the experts who have informed the Committee, as well as the manufacturers and the public. I think this was a wonderful meeting. I think it is always a great challenge, as has been articulated, and really appreciate everyone's help and expertise in thinking this through. Thank you. And safe travels.

DR. VIJH: Thank you Dr. Lynfield for chairing today's session. You did a great job. Thank you.

Thank you to all the members.

(WHEREUPON, at 2:07 p.m., the meeting concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS
Notary Public in and for the
State of Maryland

My commission expires:
Notary Registration No.:

CERTIFICATE OF TRANSCRIPTION

I, EVE JEMISON, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

_3/18/16__
Date
EVE JEMISON, CET-744
Transcriptionist